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**Original Article**

# Decrease Expression of E-cadherin in Oral Lichen Planus- A Marker of Premalignant Lesion

**Manal Rauf[1], Sumaiya Shahab[2], Shafaq Khadija [3], Ahson Ahmad[4], Henna Azmat [5], Hafsa Waseem [6] and Ahmareen Khalid Sheikh[7]**

[1,2,5,7] Department of Pathology, Shaheed Zulfiqar Ali Bhutto Medical University, Pakistan Institute of Medical Sciences, Islamabad, Pakistan, [3,6]Department of Pathology, Fazaia Medical College, Islamabad, Pakistan, [4]Department of Radiology, Shifa International Hospital, Islamabad, Pakistan.

## ABSTRACT

**Introduction:** Lichen planus is a T cell mediated disease with an unknown etiology. It has inflammation of the dermal-epidermal junction having high chances of progressing into squamous cell carcinoma. E-cadherin is responsible for maintaining cell stability and polarity and is down regulated in Lichen plannus.

**Objective:** Objective of the study is to determine the expression of E-cadherin in oral mucosal biopsies as a diagnostic aid for evaluation of malignant potential of oral lichen planus.

**Materials:** 52 samples of lichen planus were collected of clinically diagnosed patients from January to December 2019 in the Department of Histopathology, Pakistan Institute of Medical Sciences (PIMS), Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Islamabad. 16 cases comprising of normal unremarkable oral mucosa were included in control group.

**Result:** Of the total 16 specimens of normal oral mucosa, all the cases i.e. 100 % showed diffuse homogenous positivity with E-cadherin .On the other hand, all of the 52 cases of OLP showed heterogeneous pattern of staining with E cadherin, out of which, 25 cases (48%) showed 3+ score with E-cadherin, 15 cases (28.8%) showed 4+ score and 12 cases (23%) showed 2+ score.

**Conclusion:** E-cadherin showed diffuse homogeneous staining with normal mucosa and partial heterogeneous pattern on Lichen planus, showing that E-cadherin may play a significant role as a marker of malignant potential of lichen planus.

**Key words:** Oral lichen planus; E-cadherin; squamous cell carcinoma; staining pattern

## Introduction

Oral lichen planus (OLP) is a premalignant lesion of oral cavity which can cause oral squamous cell carcinoma if not diagnosed at the right time. It is a T cell mediated disease of unknown etiology [1], which damages the basal cell layer of epidermis. Histologically, it is characterized by band like inflammatory infiltrate at dermal-epidermal junction with basal cell vacuolization.

WHO has categorized this lesion as potential malignant lesion due to its progression to squamous cell carcinoma which is the most alarming complication [2,3].

**CORRESPONDENCE AUTHOR**

**Shafaq Khadija**

Department of Pathology, Fazaia Medical College, Islamabad, Pakistan

House 3A, Street 56, F-7/4, Islamabad.

Email: shafaqkhadija4@gmail.com

OLP may progress to squamous cell carcinoma. Oral squamous cell carcinoma accounts for more than 90 percent of all head and neck tumors [4]. The incidence of squamous cell carcinoma of the oral cavity has drastically increased in the past 10 years. Lips, palate (especially hard palate), tongue, buccal mucosa, trigone and floor of the mouth are the main sites for oral squamous cell carcinoma [5]. Tobacco, persistent inflammation, certain viruses, bacteria, genetic mutations, immuno-compromised state and a diet low in fibers, vegetables and fruits are thought to be the pathological factors for causing oral squamous cell carcinoma [6,7,8,9]. The risk of malignancy in oral lichen planus is 0.4 to 0.5 % over a period of 4 years [10].

It has been proved through various researches that inflammatory mediators cause the basal cell proliferation. This leads to the activation of various biological pathways of tumorigenesis [11].

E-cadherin is one of the most important intercellular adhesion molecules. It forms an E-cadherin -β-catenin

complex which is linked to the cellular actin cytoskeleton [12]. It has a major role in the stability of cellular polarity and adhesion thus maintaining the integrity of epithelial tissues [13, 14]. Downregulated expression of E-cadherin destroys its function and leads to epithelial mesenchymal transition (EMT) which causes tumorigenesis.

The rationale of this study is to determine the expression of E-cadherin in oral mucosal biopsies as a diagnostic aid for evaluation of malignant potential of oral lichen planus. As most of the biopsies are small and scanty material is available, this study may prove to be beneficial in early diagnosis of oral squamous cell carcinoma and its management.

## Materials and Methods

After getting approval from the Ethical Review Board, Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), this retrospective cross sectional study was conducted in the Department of Histopathology, Pakistan Institute of Medical Sciences (PIMS),(SZABMU), Islamabad, Pakistan. It was done over a period of one year from January to December 2019. Based on the inclusion criteria, all biopsies and resection specimens of all age groups with histological diagnosis of oral lichen planus were included as well as biopsies with unremarkable oral mucosa. Strict patient confidentiality was maintained while collecting the samples and analyzing data. All post chemotherapy biopsies and lesions other than lichen planus were excluded. The samples were then collected and evaluated at the Department of Pathology, PIMS. After fixing the specimens in 10% formalin for at least minimum period of 6 to 8 hours up to 24 hours, gross examination was done following AJCC protocols. This was followed by sectioning, processing, embedding, tissue cutting up to 3um and preparation of slide. All these slides were then stained in the laboratory with Hematoxylin and Eosin (H & E) dyes. All of these were then examined under light microscope by two surgical pathologists having a minimum of 5 years post-fellowship experience. Clinicopathological correlation was also done

For immunohistochemistry, four micron thick sections of the blocks were made. The heat induced method was adopted for antigen retrieval. Immunohistochemical stains were applied for E cadherin and examined under light microscope and reviewed by three pathologists. E-cadherin (36B5) is a mouse anti-human monoclonal antibody produced by automated LEICA system. All parameters, staining pattern, intensity and proportion of E cadherin were noted. The pattern of E cadherin expression was either diffuse positive showing homogenous staining of the cell membranes or abnormal positive showing partial (heterogeneous) staining of the cell membranes. The staining proportion was based on the percentage of cells stained as shown in Table-1. The staining intensity was either weak or strong.

**Table 1: Interpretation of E-cadherin score**

| Percentage of cells showing expression | Interpretation |
|---|---|
| < 10 % | 1+ |
| >10 to 20% | 2+ |
| 20 to 50% | 3+ |
| >50% | 4+ |

Following the inclusion and exclusion criteria, a total of 52 samples of lichen planus were collected from already clinically diagnosed patients for lichen planus. The control group had a total of 16 cases comprising of normal unremarkable oral mucosa. None of the patients had been given any sort of treatment before the sampling.

## Results

Out of the total 16 specimens of normal oral mucosa, all the cases showed diffuse homogenous positivity with E-cadherin (100%). On the other hand, all of the 52 cases of OLP showed heterogeneous pattern of staining with E cadherin, out of which, 25 cases (48%) showed 3+ score with E-cadherin, 15 cases (28.8%) showed 4+ score and 12 cases (23%) showed 2+ score . There was no case with score of 1+ as shown in Table 2.

**Table 2: Distribution of cases of Lichen planus based on E-cadherin score**

| E cadherin score | No. of cases | Percentage |
|---|---|---|
| 1+ | 0 | 0.0 |
| 2+ | 12 | 23.1% |
| 3+ | 25 | 48.1% |
| 4+ | 15 | 28.8% |

Out of the total 52 cases of lichen planus there were 50% males and 50% females (26 cases each) and their ages ranged from 11 to 78 years with a mean age of 34.7 years. Out of the 16 normal cases, there were 8 males and 8 females (50% each) and their ages ranged from 15 to 70 years with a mean age of 35 years. Moreover, 29 cases (55.8%) were in age group 21-40 years which was the most common age group

observed among the patients of LP. This is followed by the age group 1-20 years which included 12 patients (23%)

## Discussion

OLP is an inflammatory disease which is T cell mediated.CD8+ cytotoxic T cells cause the destruction of basal cells of the oral epithelium by mainly targeting the basal keratinocytes [15]. The prevalence of this disease is 0.5-2.6% in Indian population[16]. The lesions appear as white lacy plaques on the oral mucosa and tongue [17] and can progress into oral squamous cell carcinoma at a transformation rate of 0.34 to 0.69% per year [18].

In our study, the male to female ratio was 1:1 in both the control group and the LP group. No gender predilection was seen. This is similar to a few other studies, for instance, Cascone et al. from Italy [19] also observed equal proportion between males and females. Divya et al. from India [20] observed a slight male preponderance of 53% as compared to 47% females. On the other hand, some studies have shown female preponderance of Lichen Planus for example, Dastgir et al from Pakistan [21] and Siddhart et al. and Gillani et al. from India [22] observed 67% and 68% female proportion among their cases respectively. Similarly, Aleksejuniene from Canada [23] observed 81% females and only 19% males among their cases. Bautz et al. from Brazil [24] and Kaomongolkit et al. from Thailand [25] also observed a predominance of females with 80% and 73.5% females respectively.

Most common age group in our study was 21-40 years while the mean age was 35 years. When we compare this data with other studies, we observe that Divya et al. [19] and Bhattacharya et al. [26] from India also observed the same age group 20-40 years with the most common cases. However, Kaomongolkit et al. from Thailand [25] showed a mean age of 56.4 years with the most common age group being 50-70 years. Pritam et al. from India [24] showed the most common age group to be 40-49 years with a mean age of 45 years. Bautz et al. from Brazil [24] observed a mean age of 47.5 years with 40-60 years being the most common age group. We concluded from this data that there is an incidence of early OLP onset in the eastern region of the world.

With regards to the expression of E-cadherin, we observed a significant difference between the staining patterns of lichen planus and that of the control group. All the cases from the control group showed diffuse homogenous staining of the cell membranes with E-cadherin. On the other hand, the cases of Lichen planus showed partial heterogeneous staining of cell membranes with E-cadherin. Keeping in mind the diffuse staining of normal mucosa and the low staining pattern observed in squamous cell carcinoma, we can conclude that the heterogeneous pattern of staining in lichen planus is an indication that the mucosa has lost its normal histology and is moving towards dysplasia and carcinoma. Thus this partial heterogeneous staining with E cadherin can be regarded as an indicator of malignant potential in Lichen planus.

When comparing our results with other studies, we observe similar findings in international literature. Boccelino et al. from Italy [27] also observed negative staining pattern in Lichen planus as compared to the diffusely positive pattern among the control cases. Similarly, Hamaleinin et al. from Finland [28] also observed weaker E cadherin staining intensity among the cases of Lichen planus as compared to the normal mucosa. Neppelberg et al. from Norway [29] also concluded that E cadherin expression is lost as the mucosa changes from normal and moves towards Lichen planus. Yong Du et al. from China [30] also showed similar results with weak expression of E cadherin among the cases of oral lichen planus, thus suggesting that the loss of E cadherin could be an indicator of malignant potential.

With respect to the staining scores, we observed 15 cases with 4+ score. These cases were histopathologically very similar in appearance to the normal mucosa as they did not show the characteristic lichen planus like features. This led to some inter-observer disagreement among the investigating pathologists in correctly identifying the lesion on H &E sections. However, partial and heterogeneous expression of E-cadherin was very helpful in ruling out the normal mucosa.

The most commonly observed staining score in our study was 3+, having a total of 25 cases (48%). These cases were unanimously given the score of 3+ by all the pathologists and residents with no ambiguity between anyone.

## Conclusion

To conclude E cadherin staining can be an indicator of the malignant potential of Lichen planus. It can be used to evaluate the chances and speed of progression of lichen planus to carcinoma.

**Conflicts of interest:**

The authors declare no conflict of interest.

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| CONTRIBUTION OF AUTHORS | |
|---|---|
| **Author** | **Contribution** |
| Manal Rauf | A, B, C |
| Sumaiya Shahab | B, C |
| Shafaq Khadija | A, B |
| Ahson Ahmad | B, C |
| Henna Azmat | B |
| Hafsa Waseem | C |

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A. Conception/Study/Designing/Planning
B. Active Participation in Active Methodology
C. Interpretation/ Analysis and Discussion