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The expression of p53, ki67 and COX-2 in erosive-type oral lichen planus

Sayf Aziz[1], Shehab Hamad[2*], Yosra Qasim[3]

[1] Department of Oral Diagnosis, College of Dentistry, Hawler Medical University, Erbil, Iraq
[2] Kurdistan Higher Council of Medical Specialties, Erbil, Iraq
[3] Department of Pathology, College of Medicine, Hawler Medical University, Erbil, Iraq

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ABSTRACT

Oral lichen planus is a chronic inflammatory disease that affects the oral mucosa and may undergo malignant changes, which can be reflected in the expression of specific proteins that are responsible for maintaining cellular mitosis and apoptosis. The study aimed to investigate the expression of p53, ki67, and COX-2 in erosive lichen planus using immunohistochemistry to correlate these findings with the histological aspects of the disease. Thirty-three biopsies of erosive lichen planus were collected and diagnosed based on histological and clinical criteria. The blocks were processed for immunohistochemistry to assess p53, ki67, and COX-2 expression in the basal layer, suprabasal, and inflammatory infiltrate respectively. The histological analysis of the samples showed no dysplasia or metastasis. P53 stained positively in 80% of the samples, while ki67 was positive in all the cases, ranging from 5% to 85% positivity. COX-2 expression ranged from 0-50% positivity. The highest expression of p53 was observed in 8 cases (24.2%), with a maximum of 5%, and ki67 exhibited the highest expression of 90% in 3 cases (9.1%). COX-2 was negative in 27 cases (81.8%) and positive in 6 cases (18.1%), with the highest expression at 50% in 1 case and 10 % positivity in 4 cases (12.1%). In our study, the markers p53, ki67, and COX-2 proved to be useful for detecting the proliferative, inflammatory, and physiologic states of the keratinocytes. However, they did not demonstrate utility in detecting any malignant transformation.

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Introduction

The oral lichen planus is a chronic mucocutaneous disease that affects both the skin and the oral mucosa (1). It is main cause is still unknown, but it is believed to be an autoimmune defect where the inflammatory cells attack the normal epithelial keratinocyte cells. This results in the death of these cells, leading to variable defects in the skin and oral mucosa.

Clinically, oral lichen planus presents in various ways, but it can mainly be divided into non-symptomatic types, including reticular, plaque type, and macular type, and symptomatic types including atrophied, erosive type, and ulcerative types. The actual prevalence of lichen planus is not well-determined. Some articles suggest a range between 0.4% and 1% (2), while others believe it affects around 1% of the general population. Estimates between 0.14% and 1.27% have been reported worldwide, according to Daoud (3).

The association of oral lesions with skin lesions is around 60%, according to Cheng (4). However, the presence of oral lichen planus lesions accompanied by skin lesions is found in less than 16% of the cases (5).

It predominantly affects women more than men between the ages of (25-65) (6), although other studies show varying age ranges, starting from 13 years to 82 years (7).

The most common site for intraoral lesions is the buccal mucosa, where they are bilaterally presented, followed by the tongue and gingivae. The palate is the least common site to be involved. Discomfort ranges from simple itchy lesions to a burning sensation in the larger atrophied or ulcerative lesions (8).

Diagnosing an oral lichen planus lesion must be done microscopically via biopsy for the defined lesions, which will be confirmed under the microscope by showing a band-like layer of inflammatory cells extending along the basement membrane in the connective tissue. Sometimes, it also shows inflammatory cell infiltration in the basal layer, causing apoptosis of the basal keratinocytes (4).

The expression of p53 is one of the biomarkers widely used for assessing the potential malignancy of many oral lesions, including oral lichen planus (9). p53 is a protein encoded by the Tp53 gene. Under normal circumstances, its function is to produce regular p53 to stop the cell growth cycle and or promote apoptosis. However, in most human head and neck cancers, mutations in the Tp53 gene have been observed (10).

The action of p53 depends on the extent and type of cellular DNA damage (11). If the DNA damage can be repaired, the cell will continue the cell cycle. If there is no capacity to fix the DNA, the apoptotic function of p53 will be activated to stop the growth of DNA-damaged cells and prevent them from passing the damaged DNA to future cells (12).

Moreover, the amount of p53 expression can be related to a large number of cells that have been damaged in oral

* Corresponding author. Email: shehab.ahmed@hmu.edu.krd

lichen planus or due to malignant transformation, such as genotoxic stress or binding to cellular or viral oncoproteins (13).

Ki67 is an antigen that was coming across at the beginning of the 1980s by Scholzer and Gerdes (14). The Ki67 protein owns a half-life of only ~1-1.5 hours. It is active in most phases of the cell cycle (G1, S, G2 and M) but does not exist in resting cells (G0). In the later phases of mitosis (during anaphase and telophase), there is a remarkable decrease in ki67 expression (15). Ki67 is still being used as an essential marker for evaluating the cancer aggressiveness because its expression is correlated with proliferative activity of the malignant cell population (16).

Regarding oral lichen planus, Ki67 has been found as a valuable marker in assessing the proliferative activity of the cells in malignant lesions. As shown in (17), more than 40% of oral lichen planus cases stained positive for ki67 in more than 50% of the basal layer. In contrast, the suprabasal cells stained positive for ki67 in less than 9 % of the 10 cases, leading to the belief in the possibility of enhancing the chances for cancer development through epithelial cell proliferation as an attempt to sustain the epithelium integrity.

Cyclooxygenase is the common name for prostaglandin-endoperoxide synthase, an enzyme essential for converting arachidonic acid to prostaglandins. The two well-known isoforms are named as COX1 and COX-2, based on the time of their discovery (18). Regarding the COX-2 upregulation and it is relation to malignant transformation, research has found that the high expressions of COX-2 and MMP-7 are closely related to the biological behavior of oral squamous cell carcinoma. It is suggested that MMP-7 may be activated by COX-2, leading to the invasion and metastasis of OSCC (19). However, Neppelberg and Johannessen (20) have proposed that COX-2 expression is not a reliable marker for detecting malignant transformation in oral lichen planus.

Materials and Methods

The study included 33 patients diagnosed with erosive lichen planus based on the clinical and histopathological basis, patients who were under medication that could cause lichenoid reaction were excluded, 7 samples were fresh biopsies obtained from the patients complaining of their oral lesions after giving verbal consent, anesthesia was given and incisional biopsy was done and sutured as shown in Figure 1, the incised tissue was placed in 10% diluted formalin and sent to the histopathological lab in PAR Hospital Erbil while the rest 26 were retrieved from the Rezgary central lab and Al-Mufty Lab in Erbil City, The samples were prepared for staining with p53, ki67 and COX2 according to the staining protocol of the DAKO EnVision FLEX manufacturer.

For the immunohistochemical staining for p53, ki67and COX2 the following procedure was performed, for the target retrieval the mounted formalin-fixed, paraffin-embedded tissue sections were immersed into the pre-heated EnVision FLEX Target Retrieval Solution in PT Link tanks and incubate for 30 minutes at 97 °C. The sections were washed with wash buffer (DAKO omnis), the primary antibody was applied for 20 minutes and then washed again with wash buffer, the endogenous enzyme was blocked by using EnVision FLEX peroxidase blocking reagent for 3 minutes then washed again with washing buffer followed by the secondary reagent EnVision FLEX + Mouse LINKER for 10 minutes, The slides were washed again with wash buffer and then labeled polymer was applied (EnVision FLEX\HRP) for 20 minutes then washed with wash buffer and chromogen substrate was applied by adding working solution (EnVision FLEX Substrate) for 5 minutes and wash after that with wash buffer, for the counter staining a hematoxylin was applied for 3 minutes and then washed by deionized water followed by a wash with wash buffer. Each slide rack was removed with the slides from the unloading station and transferred to fresh deionized water, the racks with the slides were dehydrated, cleared and mounted with permanent mounting and the slides were coverslip.

The staining interpretation regarding p53 and ki67 was assessed microscopically with different magnification powers ranging between (10x-20x), but the intensity of the stain was neglected. The interpretation based random counting of 300 keratinocytes in the basal layer, suprabasal and submucosa, the keratinocytes' nucleus showing the brown stain is considered positive and the percentage of the expression of the satin was executed by dividing the total cells showing the stain by the total cells counted in the slide estimated by well-experienced pathologist. The slides that did not show the stain were considered negative. For COX-2 the criteria were based on the brown stain showing in keratinocyte cytoplasm and the total cells showing the stain divided by the total epithelial cells count in the slide.

For the positive and negative control, we used reactive lymph nodes to assess ki-67 immunostain positivity in germinal centers. For p53, sections from p53-positive ovarian cancers were employed, and for COX-2 immunostaining, cases of COX-2-positive colon cancer in the paraffin blocks were utilized. These cases had previously been evaluated in a study demonstrating COX-2 expression in colon cancer.

Statistical Analysis

For the data analysis. Coefficient of variance, Spearman or Pearson correlation coefficient, Kruskal-Wallis Test and Wilcoxon Signed Related- Samples Rank Test were used, for testing the significance between the age and the staining positivity we used Chi-Square test, all the tests were carried out using the statistical package for the social sciences software (SPSS) version 26.0 for windows (IBM, Chicago, IL, USA). Interdependence between immunohistochemical stains or with clinical parameters including

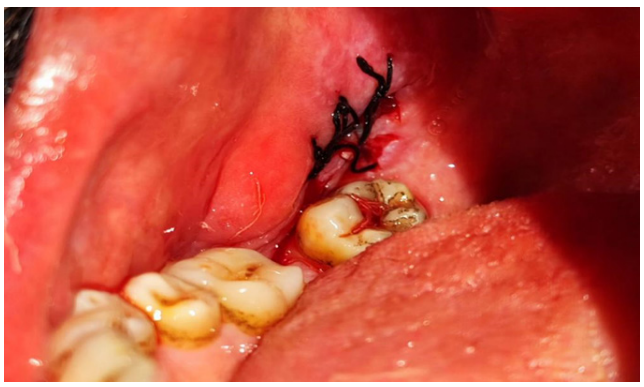

Figure 1. The biopsy site of buccal mucosal-lichen planus.

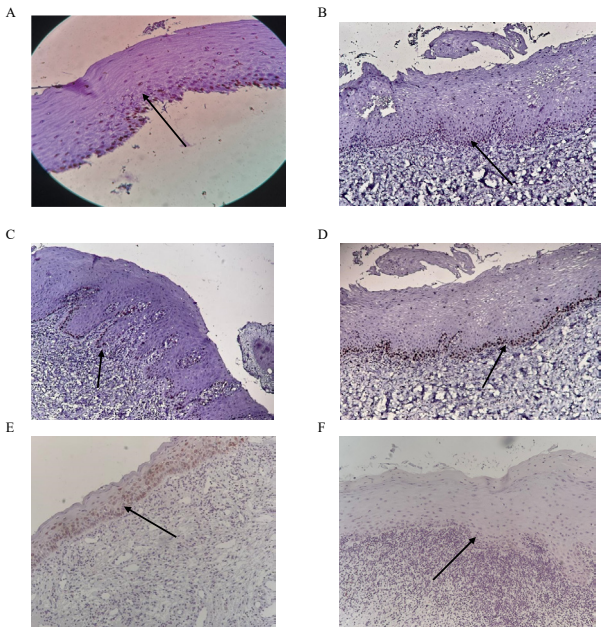

Figure 2. The top right and left photos show basal keratinocytes stained with p53 at 25% at 20x, in (A) while in (B) it is 90% at 10x. The middle left and right photos show keratinocytes stained positive with ki67 with 90%(C) and 50% (D), all at 10x. The bottom right and left photos show keratinocytes stained positive for COX-2 (E) and negative for COX-2(F). Magnification at 10x.

age and gender were considered only in situations where statistical significance was reached or almost reached. A p-value <0.05 was considered as statistically significant.

Results

The number of the cases included is 33 cases, the female percentage was 60.6% (20 cases), and the male percentage was 39.4% (13 cases) as shown in Table 1. The age ranged from 20 – 76 years old, the mean age was 48.97 and the standard deviation of 16.590. The histopathological report for all 33 cases demonstrated the presence of band-like lymphocytic infiltration at the dermo-epidermal junction, along with hyperkeratosis, acanthosis, and parakeratosis. There was no dysplasia or metastasis observed (Figure 2).

the p53 stain ranged from zero to 80% positive, the ki67 stain was found in all the cases, with a range from 5% to 85% positive, while COX-2 ranged from 0-50% positive, as shown in Table 2.

The statistical analysis of the p53 stain was found to be negative in 9 cases (27.3%) and positive in the basal and parabasal layer of 24 cases (72.7%). The most notable percent for p53 expression was 5% in 8 cases (24.2%), followed by 10 % expression in 7 cases (21.2%). The remaining percentages of p53 positivity are illustrated in Table 3.

For ki67 stain, the statistical analysis revealed that ki67

Table 1. Sex distribution of erosive oral lichen planus.

		Gender			
		Frequency	Percent	Valid Percent	Cumulative Percent
	female	20	60.6	60.6	60.6
	male	13	39.4	39.4	100.0
	Total	33	100.0	100.0	

Table 2. The expression of p53, ki67 and COX2 according to age.

	Descriptive Statistics								
	N	Range	Minimum	Maximum	Mean	Std. Deviation	Variance	Skewness	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	%C.V.
Age	33	56	20	76	48.97	16.590	275.218	-.149	
P53	33	80.00%	0.00%	80.00%	15.6061%	21.16740%	448.059	1.662	135.68 *
Ki67	33	85.00%	5.00%	90.00%	24.5455%	29.85286%	891.193	1.379	121.64 **
Cox2	33	50.00%	0.00%	50.00%	3.3333%	9.57427%	91.667	4.035	287.38

Table 3. The frequency of expression of P53.

		P53-test			
		Frequency	Percent	Valid Percent	Cumulative Percent
Percentage	0.00%	9	27.3	27.3	27.3
	5.00%	8	24.2	24.2	51.5
	10.00%	7	21.2	21.2	72.7
	15.00%	1	3.0	3.0	75.8
	25.00%	2	6.1	6.1	81.8
	50.00%	4	12.1	12.1	93.9
	60.00%	1	3.0	3.0	97.0
	80.00%	1	3.0	3.0	100.0
	Total	33	100.0	100.0	

was positive in all the cases. The least expression of 5% was seen in 14 cases (42.4%) followed by 10% in 8 cases (24.2%), while the highest expression of ki67 was 90% seen in 3 cases (9.1%). The other percentages of ki67 positivity are shown in Table 4. The COX-2 statistical analysis showed that it was negative in 27 cases (81.8%) and positive in 6 cases (18.1%). The highest expression percentage was 50% in 1 case (3%), followed by 20 % positivity in 1 case (3%), and 10 % positivity was seen in 4 cases (12.1%) as illustrated in Table 5.

The median distribution between p53 and ki67 and p53 and COX-2, was both significantly different (p = 0.001), while for the p53 and COX-2, the p-value was (p=0.000). For ki67 and COX-2, the median distribution showed a significant difference in a p-value (p= 0,000). Regarding the expression of p53, ki67 and COX-2 in the age group less than 40 years old, it showed no significant difference with a p-value > 0.05 as shown in Table 6. However, for the age group above 40 years old, it showed that there is a significant difference between the age and the positive stain of p53, ki67 and COX-2 with p-value <0.05 as shown in Table 7**.**

Discussion

Firstly, in our study, oral lichen planus was found to be more in females than in males, with a percentage of over 60% for females. This result is consistent with findings from Cheng et al (6) & Raj (7). Moreover, our study indicated that there were no signs of malignant transformation or dysplastic changes, aligning with other studies like (21) and (9). This outcome could be attributed to cultural factors, including dining habits, alcohol consumption, and smoking.

Gender did not appear to have any effect on the expression of p53, ki67 and COX-2, which agrees with most studies except for Itoh (22) who found that p53 was more strongly expressed in males than in females.

Table 4. The frequency of expression of ki67.

		Ki67-test			
		Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Percentage	5.00%	14	42.4	42.4	42.4
	10.00%	8	24.2	24.2	66.7
	15.00%	1	3.0	3.0	69.7
	25.00%	1	3.0	3.0	72.7
	30.00%	1	3.0	3.0	75.8
	50.00%	2	6.1	6.1	81.8
	70.00%	2	6.1	6.1	87.9
	80.00%	1	3.0	3.0	90.9
	90.00%	3	9.1	9.1	100.0
	Total	33	100.0	100.0	

Table 5. The frequency of expression of COX-2

		Cox2-test			
		Frequency	**Percent**	**Valid Percent**	**Cumulative Percent**
Positivity percentage	0.00%	27	81.8	81.8	81.8
	10.00%	4	12.1	12.1	93.9
	20.00%	1	3.0	3.0	97.0
	50.00%	1	3.0	3.0	100.0
	Total	33	100.0	100.0	

Table 6. The expression of pP53, ki67 and COX-2 in patients under 40 years of age.

	Test Statistics			
	Age	**P53-test**	**Ki67-test**	**Cox2-test**
Chi-Square	2.667[a]	1.000[b]	5.000[b]	4.667[c]
df	6	5	5	2
Asymp. Sig.	0.849	0.963	0.416	0.097

Table 7. The expression of pP53, ki67 and COX-2 in patients over 40 years of age.

	Test Statistics			
	Age	**P53-test**	**Ki67-test**	**Cox2-test**
Chi-Square	3.500[a]	13.333[b]	22.667[b]	31.750[c]
df	14	6	6	2
Asymp. Sig.	0.998	0.038	0.001	0.000

There is still a significant body of literature addressing the malignant transformation of oral lichen planus, with the World Health Organization categorizing oral lichen planus as a "precancerous" condition which is "a generalized state associated with significantly increased risk of cancer" (23).

The malignant transformation in oral lichen planus is widely controversial. As seen in the study done by Raj (7), they reported that six patients out of 723 cases (0.8%) of erosive type of oral lichen planus transformed into squamous cell carcinoma. In contrast, S. Irani reported that the average rate of malignant transformation could be between 0 and 10% (9), (24).

For that purpose, the use of immunohistochemical technique with biomarkers, including p53, ki67 and COX2, is essential in detecting early malignancy or malignant transformation by assessing the proliferation rate of the keratinocytes and the expression of the apoptotic regulatory proteins (Fas, Fas-L, Bcl-2, Bax, p53) (24).

However, even if no dysplastic changes were noted in our sample, the results revealed a significant controversy concerning age and the expression of p53, ki67, and COX-2, particularly in the age groups of less than 40 years and those above 40 years. Significance was found in the expression of p53, ki67 and COX-2 in relation to the age above 40 years.

Ki67 positivity was found in all the samples included in the study, with percentages ranging from (5%) in 14 cases and (to 90%) in 3 cases. Since no dysplastic changes were observed, we can suggest that this high proliferative activity of the keratinocytes is an attempt to regain the original normal histological pattern of the oral epithelium, including cellular and morphological patterns.

COX-2 is a 72-kDa inducible enzyme that plays a major role in prostaglandin production. As mentioned above, it has shown particular upregulation in oral squamous cell carcinoma (25), (26). Besides, other chronic inflammatory oral diseases like gingivitis, periodontitis, and apical periodontitis also show high expression of COX-2 (27). In oral lichen planus, there is a correlation between the severity of the oral lichen planus lesion and COX-2 upregulation (28).

Regarding COX-2, we found that it is mostly negative in most cases (81.8%), while a higher percentage of positivity was found in older patients above 40 years old. The positive expression ranged between (10% in 4 cases) and (50% in 1 case). This result can be interpreted as a strong relation between COX-2 and the chronic inflammation of the oral lichen planus, which partially agrees with Sanketh et al (29), as they showed that COX-2 expression is more intense in oral lichen planus and epithelial dysplasia, "suggesting high cell proliferation in dysplasia and chronic inflammatory reaction in lichen planus".

In our study, the p53 appeared to be positive in more than 70% of the cases, which agrees with Itoh (22). However, their most frequent positive percentage was 45%, while in our study, 5% positivity was most frequently evident. This result may be attributed to the fact that they included lichen planus cases of different clinical presentations, with the majority of them showing erosive lichen planus. in our study, we included only the erosive type of lichen planus, in which some of the keratinocytes may be lost or damaged due to the potent inflammatory reaction.

According to Itoh (22), the wild type of p53 cannot be easily found in cases of chronic inflammation, as it is half-life is between (6-20) minutes. So, it is suggested that this detected type of p53 could be mutated, as it has a half-life of more than 6 hours. However, this suggestion cannot be taken into consideration, as the upregulation of p53 in oral lichen planus appears not to be due to gene mutation but may be a physiologic action in response to the proliferative condition, a protective mechanism that would stop the cell cycle to allow repairing the damaged DNA or triggering apoptosis (30), this explanation is more accepted in our study since there is no dysplasia or metastasis found in our cases.

Conclusion

In our study, P53, ki67, and COX-2 markers demonstrated their utility in detecting the proliferative, inflammatory, and physiologic states of the keratinocytes in erosive lichen planus. However, they did not prove to be useful in detecting any malignant transformation.

We recommend that cases with higher percentages of p53, ki67 and COX-2 positivity be followed up. Further investigations in the future are necessary to determine the best marker for detecting early malignancy in oral epithelial mucosa.

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