Original Article

Expression of survivin and p53 in oral lichen planus, lichenoid reaction and lichenoid dysplasia: An immunohistochemical study

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Abstract

Context: The malignant transformation potential of oral lichen planus (OLP) and related lesions is a subject of great controversy.

Aim: The aim of this study was to compare the expression of proteins related to apoptosis and tumour suppressor gene processes in OLP, oral lichenoid reaction (OLR) and oral lichenoid dysplasia (OLD).

Materials and Methods: The immunohistochemical study was carried out to investigate the expressions of survivin and p53 in a total of 30 lesional biopsy specimens - 10 cases each of OLP, OLR and OLD. The expression rates were further compared with 10 control specimens of normal oral mucosa (NORM).

Results: Immunoreactivity for p53 was seen in 7 cases (70%) of OLD, 4 cases (40%) of OLP and 2 cases (20%) of OLR and none of NORM. We obtained a significant difference ($P = 0.01$) in mean p53 expression between the different entities. The positive staining rate of survivin was found to be significantly different between OLD (50%), OLP (10%), OLR (0%), and normal mucosa (0%) ($P = 0.004$). There was a positive correlation between p53 and survivin expression in OLP and OLD using Pearson's correlation coefficient.

Conclusion: Lichenoid dysplasia has shown p53 and survivin expression in the range of not OLP, but leukoplakia. On the other hand, OLR seems to be an innocuous lesion. The study results with OLP are inconclusive but points toward a small but important malignant potential in OLP. This kind of comparative study highlights the importance of biopsying OLP and related lesions for proper diagnosis and appropriate management.

Keywords: Oral lichen planus, oral lichenoid dysplasia, oral lichenoid reaction, P53, survivin

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INTRODUCTION

Oral lichen planus (OLP), lichenoid reaction and lichenoid dysplasia are three lesions with close clinical and histological resemblances, yet differ in their etiology, pathogenesis and biological behavior.

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Lichen planus (*leichen;* Greek, meaning "tree moss," *Planus*; Latin meaning "flat"), first described by Erasmus in 1869 is a lesion characterized by the presence of flat-topped, shiny, violaceous papules on flexor surfaces of skin. It also affects mucosal surfaces and most frequently the oral mucosa.[1]

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Lesions not compatible with Van der Meij's modified WHO criteria (2003) for lichen planus are considered to be lichenoid lesions.[2] These include mainly lichenoid reaction, lichenoid dysplasia and graft versus host reaction. The lichenoid lesions when induced by drugs, flavors or metallic restorations are called oral lichenoid reactions (OLR).[3,4] These lesions tend to resolve once the inciting factor is removed (although this resolution is not universal).[5] Epithelial maturational disturbance with cellular aberrations ranging from mild atypia to severe dysplasia in an otherwise lichen planus like lesion is recognized as a separate entity termed as oral lichenoid dysplasia (OLD).[6]

The possible malignant transformation of OLP and related lesions has been the subject of controversy in ongoing research and existing scientific literature. The first reported case of carcinoma arising from OLP was by Hallopeau, in 1910, following which numerous cases have been reported. However, recent retrospective studies have shown that at least a part of the reported cases of OLP turning malignant was in fact, from other lichenoid lesions.[7,8] Hence, the large difference in the malignant potentiality of OLP − 0%–12.5% may be due to the inclusion of OLD and OLR in their study groups.[9] There are very few studies where the malignant potential of these three different entities has been studied together.

Apoptosis, also termed programmed cell death, is a key component in embryogenesis and tissue homeostasis, as well as in tumorigenesis.[10] Besides the well-known pro- and anti-apoptotic Bcl-2 family proteins, another family of inhibitors of apoptosis proteins (IAPs) has recently been identified. Survivin protein (MW: 16.5 kDa) is the smallest of the known IAPs. It is a unique bi-functional protein that inhibits apoptosis by suppressing caspase-3 and caspase-7 and modulates the G2/M phase of the cell cycle through association with mitotic spindle microtubules. Mutation of survivin leads to loss of the antiapoptotic function, thus favoring the development of neoplastic clones. The role of survivin expression in the early steps of the carcinogenetic process has been studied in the uterine cervix, colon, skin and oral mucosa.[11] Survivin is rarely present in the normal adult tissue but is the fourth most highly expressed transcript in a number of common cancers.[12]

The normal p53 or wild-type p53 is primarily a tumor suppressor gene called by Lane as "guardian of genome,"since it plays a critical role in the maintenance of genomic integrity by controlling the cell cycle, DNA repair, and activation of apoptosis.[13] Aberrant expression of this gene results in the build-up of the p53 protein product within affected cells, enabling it to be detected immunohistochemically.[14] Impaired function of p53 gene or mutant p53 has been implicated in the development and progression of oral epithelial dysplasia and oral squamous cell carcinoma (OSCC).[15] Previous studies have shown mild to moderate expression of p53 in OLP and have pointed toward its high-risk potentiality.[16]

The potential of survivin and p53 as early markers of dysplasia and carcinogenesis has been demonstrated in oral leukoplakia and OSCC. Furthermore, survivin is rarely expressed in normal epithelium, making it a reliable marker of dysplastic changes. Here, we aimed to evaluate the immunohistochemical expression of p53 and survivin in OLP and related lesions and hence predict the relative risk of malignant potential of these lesions.

MATERIALS AND METHODS

The study sample included 40 formalin-fixed paraffin-embedded tissue blocks retrieved from the archives of the Department of Oral Pathology of our Dental College. The study group comprised of 10 cases each of OLP, OLR and OLD. Strict criteria were followed in selecting the three lesions since they have considerable overlap in their clinical and histopathological features. Only those OLP cases from the archives which fulfilled the modified the WHO criteria (2003) were included in the study.[2] For this clinical information was obtained from case history records of patients from the Department of Oral Medicine. Hematoxylin-eosin stained slides were reviewed by two pathologists to confirm the histologic diagnosis [Figure 1a]. The cases included as OLR in our study included only those cases which both clinically and histopathologically were consistent with a diagnosis of OLR. Clinically, either there was a positive local cause like

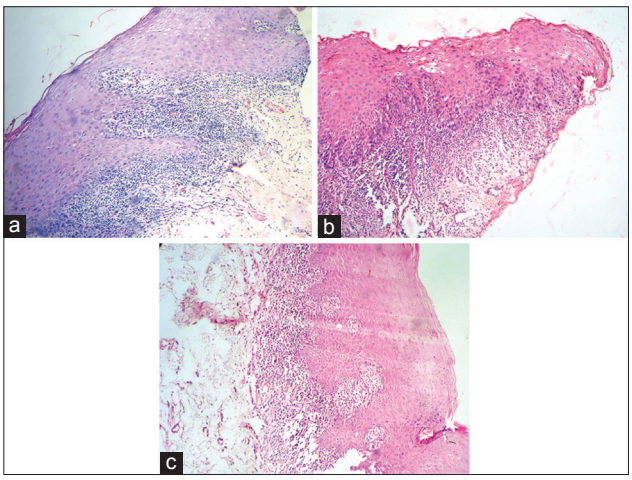


Figure 1: Photomicrographs of haematoxylin and eosin stained histological sections of (a) oral lichen planus, (b) oral lichenoid dysplasia, (c) oral lichenoid reaction (a,b,c, ×100)

amalgam restoration or positive drug history associated with the appearance of the lesions. Histopathologically, poorly differentiated lower border to subepithelial inflammatory zone; the presence of plasma cells among the lymphocytes and perivascular infiltration were taken into consideration to be per McCartan and Lamey's criteria [Figure 1c].[17] As for OLD, all diagnosis was on the purely histological basis. Lesions which clinically resembled OLP or leukoplakia, if on histopathological examination showed features of dysplasia in the epithelium, along with characteristic lichenoid features like a subepithelial band of inflammatory cells was diagnosed as OLD [Figure 1b].[6] Details of all patients' age, gender, location, clinical form of lesions,[4] and number of sites involved were recorded from previous medical and dental charts. Ten normal controls were biopsy specimens of oral mucosa of healthy individuals undergoing impacted tooth removal or preprosthetic surgery.

Immunohistochemistry

The immunohistochemical kit consisted of primary rabbit monoclonal anti-survivin (clone: EP2880Y, Biogenex Laboratories, USA) and primary mouse monoclonal anti-p53 antibody (clone-D07, Biogenex Laboratories, USA) and the Super Sensitive Polymer-HRP/DAB system (Biogenex Laboratories, USA) as the secondary antibody detection kit. OSCC tissues known to express p53 and survivin were used as an external positive control and immunostaining of OSCC sections by substituting primary antibodies with TBS were used as negative controls for each group.

Scoring and statistical analysis

For evaluation of p53 and survivin expression in the epithelium of OLP, OLR and OLD, the slides were examined under a compound microscope with eyepiece graticule at x400 magnification. Nuclei with fine to coarse brown staining, irrespective of staining intensity, were considered as positive for both p53 and survivin.[7] At least 1000 epithelial cells in areas showing maximum reactivity for p53 and survivin were counted in OLP, OLR, OLD and normal mucosa, and the number of positive cells was expressed as a percentage of counted cells. Staining of <5% of counted cells were considered as negative. Positivity of lymphocytes was not evaluated. Two investigators performed the counting-first independently and where consensus was required, the specimens were reassessed using a double-headed light microscope.

According to the statistical characteristics of our investigated data, Chi-square and one-way ANOVA were used to compare the immunostaining results of p53 and survivin in OLP, OLR, OLD and normal mucosa. The correlation between p53 and survivin expression in the three lesions was further analyzed by Pearson's correlation coefficient. The values of $P < 0.05$ were considered to be statistically significant. For all statistical analysis, Statistical Package for Social Science version 12 (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

The expressions of p53 and survivin in OLP and related lesions are listed in Table 1. The expressions of p53 and survivin were both observed as nuclear staining of varying intensity [Figures 2 and 3, respectively]. Immunoreactivity for p53 was seen in 7 of 10 cases (70%) of OLD, 4 of 10 cases of OLP (40%) and 2 of 10 cases of OLR (20%). This difference in positive staining rate of p53 between the different entities was found to be statistically significant ($P = 0.026$). The difference in mean p53 expression between the different entities was also statistically significant ($P = 0.01$). In OLR and normal mucosal sections, p53 staining was confined to the basal layer of epithelium. On the other hand, OLD and OLP

Table 1: Expression of p53 and survivin in oral lichen planus, oral lichenoid dysplasia, oral lichenoid reaction and normal oral mucosa

	p53 expression, *n* (%)	Mean p53 score	Survivin expression, *n* (%)	Mean survivin score
OLD	7 (70)	30.650	5 (50)	19.60
OLP	4 (40)	14.250	1 (10)	2.75
OLR	2 (20)	7.100	0	-
NOR	1 (10)	0.850	0	-

OLD: Oral lichenoid dysplasia, OLP: Oral lichen planus, OLR: Oral lichenoid reaction, NOR: Normal oral mucosa

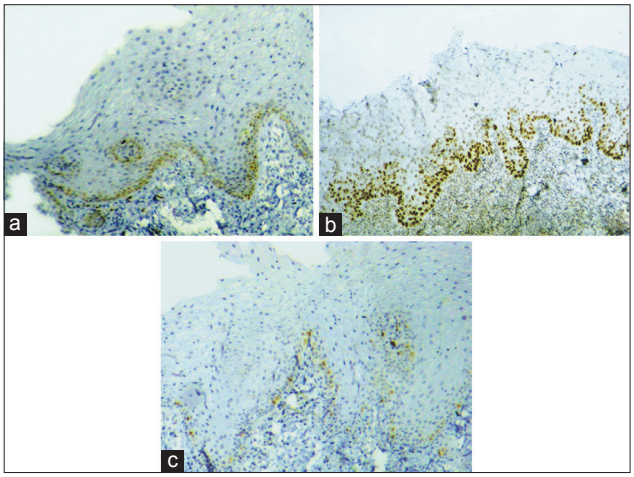


Figure 2: Immunohistochemical staining for p53. (a) oral lichen planus showing nuclear p53 expression in basal and parabasal layers of epithelium. (b) oral lichenoid dysplasia demonstrating strong nuclear p53 staining in the basal and suprabasal epithelial cells. (c) oral lichenoid reaction showing p53 staining limited to the basal layer alone (a,b,c, ×100)

demonstrated positive staining in the basal layer and lower part of the spinous layer.

The positive staining rate of survivin was found to be significantly different between OLP, OLR, OLD and normal mucosa ($P = 0.004$). Furthermore, there was a significant increase ($P = 0.003$) in mean survivin expression in OLD (19.6%) when compared to OLP, OLR and normal mucosa according to Bonferroni statistical analysis. Both OLD and OLP demonstrated positive survivin staining in the basal layer and lower half of spinous layer of the epithelium.

Of the ten cases of OLD, eight cases were clinically diagnosed with OLP and two as leukoplakia. Of the 8 cases of OLP, five and four cases showed positivity for p53 and survivin, respectively. Of the two cases where clinical diagnosis was given as leukoplakia, both cases were positive for p53 while survivin exhibited positivity in one of the cases.

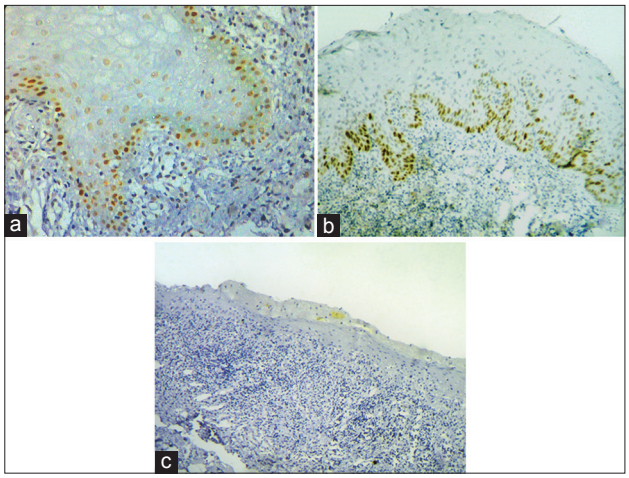


Figure 3: Immunohistochemical staining for survivin. (a) oral lichen planus showing nuclear survivin expression in basal and parabasal layers of epithelium. (b) oral lichenoid dysplasia demonstrating strong nuclear survivin staining in the basal and suprabasal epithelial cells. (c) oral lichenoid reaction showing negative survivin staining (a, ×400, b and c, ×100)

The relations of p53 and survivin expressions to the clinical parameters of patients with OLP and related lesions are summarized in Tables 2 and 3, respectively. There was no significant correlation between the expression of the two markers and the patients' age, gender, clinical form of lesions and number of sites involved.

A positive correlation was obtained between p53 and survivin expression in OLP and OLD using Pearson's correlation coefficient [Table 4]. In all cases of OLP or OLD where survivin was positive, we observed that p53 was also positive.

DISCUSSION

Oral lichen planus, lichenoid reaction and lichenoid dysplasia are three lesions with close clinical and histological resemblances [Figure 1], yet differ in their etiology, pathogenesis and biological behavior. The studies pertaining to potentially malignant nature of OLP have been largely inconclusive or give contradictory results. A recent study of OLP patients by Bombeccari *et al*. (following the modified WHO criteria), reported an annual malignant transformation rate of 0.36%.[18] As for OLR and OLD, there is a definite paucity of studies regarding their biologic behavior.

Resistance to apoptotic stimuli is frequently involved in cancer development and IAPs like survivin are believed to

Table 2: Relation between clinicopathologic features of oral lichen planus, oral lichenoid reaction, oral lichenoid dysplasia and normal and immunohistochemical expression of p53 expression

	OLP		OLR		OLD		Normal	
	Total	Positive, *n* (%)	Total	Positive, *n* (%)	Total	Positive, *n* (%)	Total	Positive, *n* (%)
Gender								
Male	3	1 (33.3)	4	1 (25)	5	3 (60)	4	1 (25)
Female	7	3 (42.9)	6	1 (16.7)	5	4 (80)	6	0
P		0.667		0.667		0.5		0.4
Age (years)								
<40	3	1 (33.3)	5	2 (40)	3	2 (66.7)	4	1 (25)
≥40	7	3 (42.9)	5	0	7	5 (71.4)	6	0
P		0.667		0.222		0.708		0.4
Site								
Single	0	0	4	1 (25)	5	4 (80)	NA	NA
Multiple	10	4 (40)	6	1 (16.7)	5	3 (60)	NA	NA
P		NA		0.667		0.5		NA
Clinical form								
Hypertrophic	6	2 (33.3)	7	2 (28.6)	5	4 (80)	NA	NA
Erosive	4	2 (50.0)	3	0	5	3 (60)	NA	NA
P		0.548		0.467		0.5		NA

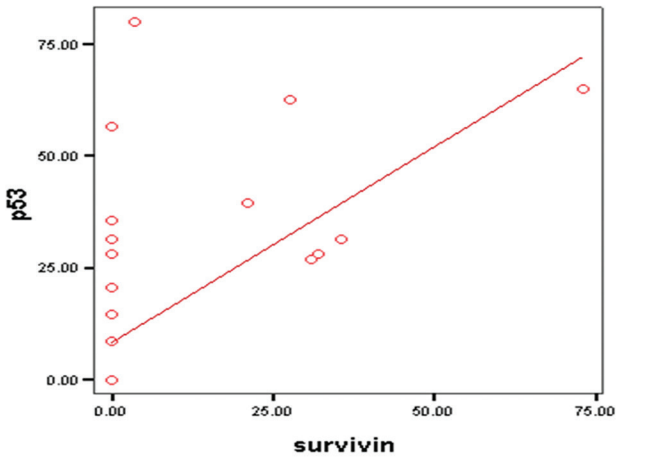
OLD: Oral lichenoid dysplasia, OLP: Oral lichen planus, OLR: Oral lichenoid reaction, NA: Not available

Table 3: Relation between clinicopathologic features of oral lichen planus, oral lichenoid reaction, oral lichenoid dysplasia and normal and immunohistochemical expression of survivin expression

	OLP		OLR		OLD		Normal	
	Total	Positive, *n* (%)	Total	Positive, *n* (%)	Total	Positive, *n* (%)	Total	Positive, *n* (%)
Gender								
Male	3	0	4	0	5	3 (60)	4	0
Female	7	1 (14.3)	6	0	5	2 (40)	6	0
P		0.7		NA		0.5		NA
Age (years)								
<40	3	0	5	0	3	2 (66.7)	4	0
≥40	7	1 (14.3)	5	0	7	3 (42.9)	6	0
P		0.7		NA		0.5		NA
Site								
Single	0	0	4	0	5	3 (60)	NA	NA
Multiple	10	1 (10)	6	0	5	2 (40)	NA	NA
P		NA		NA		0.5		NA
Clinical form								
Hypertrophic	6	1 (16.7)	7	0	5	3 (60)	NA	NA
Erosive	4	0	3	0	5	2 (40)	NA	NA
P		0.6		NA		0.5		NA

OLD: Oral lichenoid dysplasia, OLP: Oral lichen planus, OLR: Oral lichenoid reaction, NA: Not available

Table 4: Pearson's correlation coefficient. A positive correlation was obtained between p53 and survivin expression in oral lichen planus and oral lichenoid dysplasia



enable dysplastic cells to acquire this property.[19] Recent studies have found survivin expression to be increased from epithelial dysplasia to OSCC with no expression in normal mucosa.[20] The study may be considered the first study where survivin expression was evaluated in the three closely related lesions OLP, OLR and OLD. We found a significant difference in the expression of survivin in OLP, OLR, OLD and normal mucosa, with OLD exhibiting maximum expression compared to normal, OLP and OLR. The expression of survivin in OLD is in the range of the expression seen in other dysplastic lesions such as leukoplakia, OSMF and esophageal dysplasia.[11,21] However, OLR did not show any survivin expression at all. There was no survivin expression in normal mucosa which was in agreement with previous studies.[19,22,23] In contrast, Chaiyarit *et al*., have found an increase in survivin expression in normal mucosa compared to OLP, which they have attributed to confounding variables.[24]

In our attempt to elucidate the difference in p53 expression between OLP, OLR and OLD, we found a statistically significant increase in expression of p53 in OLD compared to normal mucosa, OLP and OLR. Similar to survivin, this p53 expression in OLD is in agreement with the expression in other dysplastic lesions such as leukoplakia,[15,25-27] and OSMF.[28] p53 protein has fundamental importance in maintaining the genome integrity because it allows the action of DNA repair mechanisms and the removal of damaged cells through the apoptosis process. In fact, several studies suggested that p53 mutations are essential for the initial steps of oral carcinogenesis.[29]

The expression of p53 protein in 40% of OLP cases in our study is in accordance with the previous monograph.[7,16,30] Although not statistically significant this p53 protein expression in OLP was observed to be more than OLR and normal mucosa was definitely less than OLD. Many researchers have examined the role of p53 expression in OLP and in these the immunopositivity of p53 ranged from 18% to 100%.[7,30-35] The large variation of p53 staining in OLP observed in the literature may be due to the inclusion of OLD and OLR in them, methods of antigen retrieval and different p53 antibodies used.[13] As in the case of survivin expression, OLR showed no significant difference in p53 expression from normal and a significantly less expression compared to OLD.

There was a positive correlation between p53 and survivin expression in our study. Survivin is a downstream gene in the p53 pathway, and we observed that in all cases where

survivin was expressed, p53 was also expressed. Mirza *et al*. and Hoffman *et al*. demonstrated that the cellular accumulation of wild-type p53 results in down-regulation of survivin, thus suggesting a negative feedback loop between survivin expression and wild-type p53. p53 mutations in dysplasia and carcinomas could be responsible for the failure of this negative feedback loop between wild-type p53 and survivin and thereby result in survivin accumulation with mutant p53.[18,21] Although D07 clone of p53 does not differentiate between wild-type and mutant p53[31] this positive correlation seen in OLP and OLD between p53 and survivin suggest that the p53 is indeed mutant p53 in these cases.[7]

Another important finding we noted was that in OLD and OLP there was suprabasal p53 staining, whereas in normal and OLR the staining was restricted to the basal layer alone. The expression of p53 protein in the basal layer in oral mucosa may be due to the wild-type protein induced by environmental factors that occur commonly in the oral cavity. This phenomenon might be protective; allowing keratinocytes to repair damaged DNA.[25] On the other hand, p53 expression in suprabasal cells is more suggestive of a mutant p53 showing the presence of cells with DNA damage in more superficial layers of the epithelium, rather than a cross-reactivity with wild-type.

In summary, lichenoid dysplasia has shown p53 and survivin expression in the range of leukoplakia and not OLP. Therefore, it requires an increased frequency of follow-up and management similar to leukoplakia. On the other hand, the negligible expression of p53 and survivin in OLR suggests that it is probably an innocuous lesion and is best managed, where possible, by removal of the causative agent. Our results with OLP are inconclusive but points toward a small but important malignant potential in OLP. The expression of p53 protein in OLP in our study was similar to other studies in literature, and this was determined to be mutant p53 as suggested by the positive correlation between p53 and survivin and the suprabasal location of p53. These may be indicative of a potentially increased malignancy risk in OLP. This kind of comparative study highlights the importance of biopsying OLP and related lesions for proper diagnosis and appropriate management.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Gasco M, Crook T. The p53 network in head and neck cancer. Oral Oncol 2003;39:222-31.
2. van der Meij EH, van der Waal I. Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria and suggestions for modifications. J Oral Pathol Med 2003;32:507-12.
3. McCartan BE, McCreary CE. Oral lichenoid drug eruptions. Oral Dis 1997;3:58-63.
4. Schlosser BJ. Lichen planus and lichenoid reactions of the oral mucosa. Dermatol Ther 2010;23:251-67.
5. DeRossi SS, Ciarrocca KN. Lichen planus, lichenoid drug reactions, and lichenoid mucositis. Dent Clin North Am 2005;49:77-89, viii.
6. Krutchkoff DJ, Eisenberg E. Lichenoid dysplasia: A distinct histopathologic entity. Oral Surg Oral Med Oral Pathol 1985;60:308-15.
7. Lee JJ, Kuo MY, Cheng SJ, Chiang CP, Jeng JH, Chang HH, *et al*. Higher expressions of p53 and proliferating cell nuclear antigen (PCNA) in atrophic oral lichen planus and patients with areca quid chewing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;99:471-8.
8. Lo Muzio L, Mignogna MD, Favia G, Procaccini M, Testa NF, Bucci E, *et al*. The possible association between oral lichen planus and oral squamous cell carcinoma: A clinical evaluation on 14 cases and a review of the literature. Oral Oncol 1998;34:239-46.
9. Gonzalez-Moles MA, Scully C, Gil-Montoya JA. Oral lichen planus: Controversies surrounding malignant transformation. Oral Dis 2008;14:229-43.
10. Hsue SS, Chen YK, Lin LM. Expression of survivin and XIAP for DMBA-induced hamster buccal pouch squamous cell carcinogenesis is associated with p53 accumulation. Oral Oncol 2008;44:43-9.
11. Parenti A, Leo G, Porzionato A, Zaninotto G, Rosato A, Ninfo V, *et al*. Expression of survivin, p53, and caspase 3 in Barrett's esophagus carcinogenesis. Hum Pathol 2006;37:16-22.
12. Duffy MJ, O'Donovan N, Brennan DJ, Gallagher WM, Ryan BM. Survivin: A promising tumor biomarker. Cancer Lett 2007;249:49-60.
13. Ebrahimi M, Nylander K, van der Waal I. Oral lichen planus and the p53 family: What do we know? J Oral Pathol Med 2011;40:281-5.
14. Castle JT, Cardinali M, Kratochvil FJ, Abbondanzo SL, Kessler HP, Auclair PL, *et al*. P53 and cyclin D1 staining patterns of malignant and premalignant oral lesions in age-dependent populations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999;88:326-32.
15. Ravi D, Nalinakumari KR, Rajaram RS, Nair MK, Pillai MR. Expression of programmed cell death regulatory p53 and bcl-2 proteins in oral lesions. Cancer Lett 1996;105:139-46.
16. Safadi RA, Al Jaber SZ, Hammad HM, Hamasha AA. Oral lichen planus shows higher expressions of tumor suppressor gene products of p53 and p21 compared to oral mucositis. An immunohistochemical study. Arch Oral Biol 2010;55:454-61.
17. McCartan BE, Lamey PJ. Expression of CD1 and HLA-DR by langerhans cells (LC) in oral lichenoid drug eruptions (LDE) and idiopathic oral lichen planus (LP). J Oral Pathol Med 1997;26:176-80.
18. Bombeccari GP, Guzzi G, Tettamanti M, Giannì AB, Baj A, Pallotti F, *et al*. Oral lichen planus and malignant transformation: A longitudinal cohort study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;112:328-34.
19. Lin CY, Hung HC, Kuo RC, Chiang CP, Kuo MY. Survivin expression predicts poorer prognosis in patients with areca quid chewing-related oral squamous cell carcinoma in Taiwan. Oral Oncol 2005;41:645-54.
20. Lo Muzio L, Farina A, Rubini C, Pezzetti F, Stabellini G, Laino G, *et al*. Survivin as prognostic factor in squamous cell carcinoma of the oral cavity. Cancer Lett 2005;225:27-33.
21. Zhou S, Qu X, Yu Z, Zhong L, Ruan M, Ma C, *et al*. Survivin as a potential early marker in the carcinogenesis of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:575-81.

22. Sah NK, Khan Z, Khan GJ, Bisen PS. Structural, functional and therapeutic biology of survivin. Cancer Lett 2006;244:164-71.
23. Baytekin F, Tuna B, Mungan U, Aslan G, Yorukoglu K. Significance of P-glycoprotein, p53, and survivin expression in renal cell carcinoma. Urol Oncol 2011;29:502-7.
24. Chaiyarit P, Jintakanon D, Klanrit P, Siritapetawee M, Thongprasom K. Immunohistochemical analyses of survivin and heat shock protein 90 expression in patients with oral lichen planus. J Oral Pathol Med 2009;38:55-62.
25. Abbas NF, Labib El-Sharkawy S, Abbas EA, Abdel Monem El-Shaer M. Immunohistochemical study of p53 and angiogenesis in benign and preneoplastic oral lesions and oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:385-90.
26. Agarwal S, Mathur M, Srivastava A, Ralhan R. MDM2/p53 co-expression in oral premalignant and malignant lesions: Potential prognostic implications. Oral Oncol 1999;35:209-16.
27. Fan GK, Chen J, Ping F, Geng Y. Immunohistochemical analysis of P57(kip2), p53 and hsp60 expressions in premalignant and malignant oral tissues. Oral Oncol 2006;42:147-53.
28. Trivedy C, Warnakulasuriya KA, Tavassoli M, Steingrimsdottir H, Penhallow J, Maher R, *et al*. P53 aberrations in oral submucous fibrosis and oral squamous cell carcinoma detected by immunocytochemistry and PCR-SSCP. J Oral Pathol Med 1998;27:72-7.
29. Al-Hashimi I, Schifter M, Lockhart PB, Wray D, Brennan M, Migliorati CA, *et al*. Oral lichen planus and oral lichenoid lesions: Diagnostic and therapeutic considerations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103 Suppl:S25.e1-12.
30. de Sousa FA, Paradella TC, Carvalho YR, Rosa LE. Comparative analysis of the expression of proliferating cell nuclear antigen, p53, bax, and bcl-2 in oral lichen planus and oral squamous cell carcinoma. Ann Diagn Pathol 2009;13:308-12.
31. Valente G, Pagano M, Carrozzo M, Carbone M, Bobba V, Palestro G, *et al*. Sequential immunohistochemical p53 expression in biopsies of oral lichen planus undergoing malignant evolution. J Oral Pathol Med 2001;30:135-40.
32. Acay RR, Felizzola CR, de Araújo N, de Sousa SO. Evaluation of proliferative potential in oral lichen planus and oral lichenoid lesions using immunohistochemical expression of p53 and Ki67. Oral Oncol 2006;42:475-80.
33. Gonzalez-Moles MA, Gil-Montoya JA, Ruiz-Avila I, Esteban F, Bascones-Martinez A. Differences in the expression of p53 protein in oral lichen planus based on the use of monoclonal antibodies DO7 and pAb 240. Oral Oncol 2008;44:496-503.
34. González-Moles MA, Bascones-Ilundain C, Gil Montoya JA, Ruiz-Avila I, Delgado-Rodríguez M, Bascones-Martínez A, *et al*. Cell cycle regulating mechanisms in oral lichen planus: Molecular bases in epithelium predisposed to malignant transformation. Arch Oral Biol 2006;51:1093-103.
35. Tanda N, Mori S, Saito K, Ikawa K, Sakamoto S. Expression of apoptotic signaling proteins in leukoplakia and oral lichen planus: Quantitative and topographical studies. J Oral Pathol Med 2000;29:385-93.