Original

Immunohistochemical Study of Differential Expressions of CAR, E-Cadherin, CK-13, -17, p53 and Ki-67 in Oral Lichen Planus, Lichenoid Lesion and Lichenoid Epithelial Dysplasia

Junya Ono, Yasuo Okada, Yoriaki Kanri, Hiroto Sano and Hitoshi Hasegawa

Department of Pathology, The Nippon Dental University School of Life Dentistry at Niigata, Niigata, Japan
(Accepted for publication, September 10, 2021)

Abstract: Clinically suspected oral lichen planus (OLP) includes histopathologically proven OLP, oral lichenoid lesion (OLL) or lichenoid stomatitis, and oral lichenoid dysplasia (OLD). Malignant transforming potential of OLD is a diagnostic issue. This study aimed to exclude OLD from OLP and OLL and examine the role of OLD in malignant transformation. Immunostaining for CK13, CK17, p53, Ki-67, Coxsackie–adenovirus receptor (CAR) and E-Cadherin was conducted in 200 cases. CK13-positive rate was lower in OLD (33.3%) than in OLP and OLL. CK17-positive rate was slightly lower in OLD (89.2%) compared to OLP and OLD. Ki-67-positive rate from basal to spinous layer was higher in OLD (30.6%) than in OLP and OLL, and p53 showed similar trend (OLD: 19.4%). Rate of attenuated CAR staining intensity from basal layer to lower one-third of spinous layer was higher in OLD (77.8%) compared to OLP and OLL, similar to rate of attenuated E-Cadherin staining (OLD: 45.8%). In conclusion, a diagnosis of OLP or OLL is indicated when the lesion is CK13 positive and CK17 positive, with no attenuation of staining intensity for CAR and E-Cadherin from the basal layer to the lower one-third of the spinous layer. On the other hand, a diagnosis of OLD is indicated when the lesion is CK13 negative and CK 17 positive, with attenuation of staining intensity for CAR and E-Cadherin from the basal layer to the lower one-third of the spinous layer. In OLD, attenuated CAR expression may participate in malignant transformation by weakening cell junction in the epithelium and inducing epithelial mesenchymal transition.

Key words: Oral lichen planus, Oral lichenoid lesion, Oral lichenoid dysplasia, Immunohistochemical study

Introduction

Oral lichen planus (OLP) occurs frequently on the buccal mucosa, tongue and gingiva of middle-aged and elderly women. On gross examination, OLP presents a variety of symptoms such as a reticular pattern, white striations, white papules, white plaques, atrophy, erythema, erosions, and ulcerative type (1-3). Histopathological findings of OLP are characterized by epithelial hyperparakeratosis, appearance of a granular layer, thickening of the spinous layer, serrated rete ridges, separation of the basement membrane due to liquefaction (Max Joseph spaces), and band of lymphocytic infiltration beneath the epithelium. The infiltrating lymphocytes consist of a mixture of CD4 positive and CD8 positive T cells (4,5). A small number of CD8 positive T cells infiltrate the epithelium, causing apoptosis of epithelial cells that form colloid bodies (civatte bodies). Lesions that are subjected to biopsy due to clinical findings suspected of OLP include cases histopathologically confirmed as OLP, oral lichenoid lesion (OLL) or lichenoid stomatitis (1-3,4) and oral lichenoid dysplasia (OLD) (5) (lichen planus-like epidermal dysplasia).

OLP is the oral mucosal lesion of systemic lichen planus, but the lesion may be limited to the oral cavity in some cases. The lesions generally occur bilaterally and symmetrically, although depending on the stage, unilateral and solitary lesions have been reported (2,6-12). OLL resembles OLP both clinically and histopathologically, and this lesion is considered to be associated with allergy against metals and drugs used in dentistry (1,2,7,8,11,13). OLL includes oral lichenoid contact lesion (OLCL) and oral lichenoid drug reaction (OLDR). While OLLs usually present as unilateral or solitary lesions, bilateral lesions are sometimes encountered (1,2,7,8,11,13). The histopathological differences between OLL and OLP are as follows (2,7,8,13). Compared to OLP, OLL shows strong subepithelial edematous change and diffuse inflammatory cell infiltration extending to deep sites, and the infiltrate consists of lymphocytes admixed with neutrophils, eosinophils, macrophages, and plasma cells. In addition, fibrinoid deposition may be observed on the blood vessel wall. For OLD, although this lesion manifests similar clinical symptoms as OLP and OLL, the potential association of this lesion with malignant transformation (1,3,8,14,19) is often an issue in diagnosis. Therefore, it is important to exclude OLD from OLP and OLL in differential diagnosis (14,19).

The histopathological characteristics that differentiate OLD from OLP and OLL are as follows (1,15,16). Compared to OLP and OLL, OLD has slightly thicker epithelium, and while cellular and nuclear atypia as well as loss of cell polarity are present, the basement membrane shows no liquefaction change and is maintained intact. In OLD, subepithelial lymphocyte infiltration is diffuse and extends to deep sites, similarly to OLL.

Despite the above-mentioned differences among OLP, OLL and OLD, difficulties are often encountered in clinical and histopathological diagnoses of these lesions. Therefore, understanding of the pathologies of these diseases and a method that allows easy differentiation among OLP, OLL and OLD would be useful for selecting appropriate treat-
ments for these diseases. However, while many previous studies focused on morphology and the invading lymphocytes\textsuperscript{1,2,3,7-9,13,14}, there are few reports on immunohistochemical analysis of the epithelium\textsuperscript{20-22}. With this background, we performed immunohistochemical studies on not only CK13, CK17, p53 and Ki-67\textsuperscript{23,24} that have high diagnostic value for epithelial dysplasia, but also Coxsackie-adenovirus receptor (CAR) that is associated with adhesion between epithelial cells\textsuperscript{25-30}, as well as the epithelial marker E-Cadherin that is downregulated by epithelial mesenchymal transition (EMT)\textsuperscript{31}, and examined the expression patterns of these molecules in OLP, OLL and OLD.

**Materials and Methods**

**Subjects**

We reviewed the histopathological diagnoses of the cases subjected to biopsy due to a clinical diagnosis or suspicion of OLP in the past 16 years (from February 2000 to February 2016) who were conducted at least five-year follow-up, with paraffin-embedded tissue blocks archived in our department. Two hundred cases which were confirmed histopathologically as OLP, OLL or OLD were used in the present study.

**Methods**

Immunostaining for CK13 (1:400; Dako, DE-K13, Agilent Technologies Inc., Santa Clara, CA, USA), CK17 (1:100; Dako, E3, Agilent Technologies Inc.), p53 (1:400; Dako, DO-7, Agilent Technologies Inc.), Ki-67 (1:1,000; Dako, MIB-1, Agilent Technologies Inc.), CAR (1:800; Bethyl Laboratories Inc., Montgomery, TX, USA) and E-Cadherin (1:5,000; 36/E-Cadherin, BD Transduction Laboratories\textsuperscript{TM}, San Jose, CA, USA) was performed in all the OLP, OLL and OLD cases. The expression patterns of these molecules in the epithelium were compared among the three diseases.

**Immunohistochemical staining**

From paraffin-embedded tissues, serial sections of 3 µm thickness were prepared. After deparaffinization, the sections were incubated with Immunosaver (Nissin EM, Tokyo, Japan) at 98˚C for 45 min to retrieve antigen, and then treated with ethanol containing 0.3% H\textsubscript{2}O\textsubscript{2} to block endogenous peroxidase. The sections were incubated with 5% normal goat serum (Dako) for 10 min at room temperature, and then incubated with the primary antibodies overnight at 4˚C. Then the samples were treated with secondary antibodies (Histofine Simple Stain MAX-PO MULTI, Nichirei Bioscience Inc., Tokyo, Japan) for 30 min at room temperature. 3,3’-diaminobenzidine·4HCL (DAB Substrate kit, Nichirei Bioscience Inc.) was used for color development. After nucleus staining with hematoxylin, the slides were observed under a light microscope (BX53; Olympus, Tokyo, Japan) and evaluated.

This study was approved by the Ethics Committee of The Nippon Dental University School of Life Dentistry at Niigata (ECNG-R-287).

**Results**

The histopathological diagnoses of the 200 cases were OLP in 83 cases, OLL in 45 cases, and OLD in 72 cases. The most common biopsy site was the buccal mucosa (134 cases), and other sites included gingiva, tongue, lip, gingivo-buccal fold, and palatal mucosa (Table 1). There were 63 males and 137 females, with ages ranging from 14 to 84 (mean 61.5) years. The 83 OLP cases comprised 23 males and 60 females, aged 14-84 years (mean 59.8 years), and the majority were females in the 60s and 50s (Fig. 1A). The 45 OLL cases comprised 13 males and 32 females, aged 39-84 years (mean 65.2 years), and the majority were females in the 60s (Fig. 1B). The 72 OLD cases comprised 27 males and 45 females, aged 32-79 years (mean 61.2 years), and the majority were females in the 50s (Fig. 1C). Comorbidities were as follows. The number of hypertensive patients taking antihypertensive drugs was larger in OLL (17 cases, 37.8%) than in OLP (7 cases, 8.4%) and OLD (13 cases, 18.1%). The number of dyslipidemic patients taking medications for hyperlipidemia was larger in OLL (6 cases, 13.3%) than in OLD (3 cases, 4.2%), while no patient with OLP were taking such medication. Hepatitis C was found in 1 OLL case (2.2%), 4 OLD cases (5.6%), and none of the OLP cases. Two patients with OLP (2.4%) and 1 patient (2.2%) with OLL were taking anticoagulant for cerebral infarction.

After the initial biopsy, malignant transformation occurred in 4 cases, all of which were OLD.
Figure 2. Histopathological and immunohistochemical findings. (A-H) A typical case of oral lichen planus. (A, B) H-E staining shows hyperparakeratosis of the epithelium, serrated rete ridges and subepithelial band of lymphocyte infiltration, but no epithelial dysplasia. (C) CK13 immunoreactivity is observed in the cytoplasm in all layers of the epithelium. (D) CK17 immunoreactivity is observed in the cytoplasm in all layers of the epithelium. (E) Ki-67 immunoreactivity is observed in the nuclei in the second row of the basal layer. (F) Non-continuous p53 immunoreactivity is observed in the nuclei in the basal/parabasal layer. (G) Strong CAR immunoreactivity is observed at the cell membrane in all layers of the epithelium. (H) Strong E-Cadherin immunoreactivity is observed at the cell membrane in all layers of the epithelium.

(I-P) A typical case of oral lichenoid lesion. (I, J) H-E staining shows epithelial hyperparakeratosis, subepithelial edematous change and diffuse inflammatory cell infiltration reaching the deep site, but no epithelial dysplasia. (K) CK13 immunoreactivity or patchy immunoreactivity is observed in the cytoplasm from the upper half of the spinous layer to the superficial layer. (L) CK17 immunoreactivity is observed in the cytoplasm in all layers of the epithelium. (M) Non-continuous Ki-67 immunoreactivity is observed in the nuclei in the second row of the basal layer. (N) p53 immunoreactivity is observed in the nuclei in the basal/parabasal layer. (O) Strong CAR immunoreactivity is observed at the cell membrane in all layers of the epithelium. (P) Strong E-Cadherin immunoreactivity is observed at the cell membrane in all layers of the epithelium.

(Q-X) A typical case of oral lichenoid dysplasia. (Q, R) H-E staining shows hyperparakeratosis together with epithelial dysplasia, and diffuse inflammatory cell infiltration beneath the epithelium. (S) No CK13 immunoreactivity is observed in all layers of the epithelium. (T) CK17 immunoreactivity is observed in the cytoplasm in all layers of the epithelium. (U) Ki-67 immunoreactivity is observed in some nuclei from the first row of the basal layer to the spinous layer. (V) p53 immunoreactivity is observed in some nuclei from the basal/parabasal layer to the spinous layer. (W) Attenuation of CAR immunostaining is observed on the cell membrane from the basal layer to the lower one-third of the spinous layer. (X) Attenuation of E-Cadherin is observed on the cell membrane from the basal layer to the lower one-third of the spinous layer. Scale bars: 250 µm.
Expression of p53 in the spinous layer was found in none of the 83 OLP cases (0%), 2 of 45 OLL cases (4.4%), and 14 of 72 OLD cases (19.4%) (Table 5, Fig. 2).

Expression of CAR expression was observed in OLP, OLL, and OLD cases. However, attenuation of staining intensity in cells from the basal layer to the lower one-third of the spinous layer was observed in 15 of 83 OLP cases (18.1%), 7 of 45 OLL cases (15.6%), and 56 of 72 OLD cases (77.8%) (Table 6, Fig. 2).

Expression of E-Cadherin was observed in OLP, OLL, and OLD cases, but attenuation of staining intensity from the basal layer to the lower one-third of the spinous layer was observed in 3 of 83 OLP cases (3.6%), 1 of 45 OLL cases (2.2%), and 33 of 72 OLD cases (45.8%) (Table 7, Fig. 2).

Discussion

Lesions clinically diagnosed as OLP and subjected to biopsy include histopathologically proven cases of OLP, OLL or lichenoid stomatitis, and OLD, and differentiation of these lesions is considered difficult at times. Moreover, malignant lesions are sometimes encountered, posing additional difficulties in diagnosis and treatment. To explore a useful scheme for differentiation of these lesions, we conducted histopathological and immunohistochemical studies focusing on the epithelium of these lesions.

Among the 200 cases of clinically diagnosed or suspected OLP, 83 cases were histopathologically diagnosed as OLP, 45 cases as OLL, and 72 cases as OLD. Although there are few reports on the proportions of these lesions, our findings confirm that cases clinically diagnosed as lichen planus contain many OLL and OLD cases. Therefore, diagnosis by biopsy is important not only for appropriate treatment of OLP but also for early detection of cases with potential for malignant transformation.

In the present study, the majority of patients with OLP were women in their 60s and 50s, and many patients with OLL were taking medications for hypertension and dyslipidemia, which are consistent with previous reports. Some reports showed that hepatits C virus (HCV) was involved in the development of OLP, while other report found no such involvement. In our series, hepatitis C was found in 4 OLP cases (5.6%) and 1 OLL case (2.2%), but in none of the OLD cases. Hence, the association between HCV and OLP could not be studied. As a result of hepatitis C treatment using novel drugs, negative conversion of HCV has become noticeable. The accompanying pathological change of OLP should be a topic of future study. Follow-up reports are awaited from facilities that previously reported an involvement of HCV in the development of OLP.

Cytokeratin belongs to the intermediate sized filaments of the cytoskeleton. Over 20 subtypes of cytokeratin are known and they express differentially in the normal epithelium and various epithelial tumors. Acidic keratins such as CK13, CK14, CK15, CK16, CK17 and CK19 as well as basic keratins including CK4, CK5 and CK6 have been identified on the lingual mucosal epithelium, and the expressions of these subtypes vary in different layers of the epithelium. CK13 evaluated in the present study is a high molecular weight (51 kD) keratin expressed in the parabasal layer of non-cornified stratified squamous epithelium. CK17 is a low molecular weight (46 kD) keratin expressed in the basal layer of normal epithelium. In epithelial dysplasia, reports generally show negative CK13 expression and positive CK17 expression.

In the present study, CK13 was positive in 75 of 83 OLP cases (90.4%); positive staining was observed in all epithelial layers (all-layer positive) in 16 cases (19.3%) and in some layers (partial positive) in 59 cases.
(71.1%) including 33 cases showing patchy staining. CK13 was also positive in 36 of 45 OLL cases (80.0%); all-layer positive in 4 cases (8.9%) and partial positive in 32 cases (71.1%) including patchy staining in 23 cases. In OLP and OLL, sections showing partial positive staining (including patchy staining) of CK13 contained areas of negative staining, implying that although abnormalities in stratified differentiation existed, there was no dysplasia. CK13 was positive in only 24 of 72 OLD cases (33.3%) (all-layer positive in 1 case and partial positive in the other 21 cases) and was negative in 48 cases (66.7%). The CK13 negative rate was higher in OLD than in OLP and OLL, which is consistent with previous reports for epithelial dysplasia in general. Thus, findings of CK13 immunostaining may not be useful to exclude OLD from OLP and OLL.

On the other hand, CK17 was positive in 74 of 83 OLP cases (89.2%) including all-layer positive in 63 cases (75.9%), in 44 of 45 OLL cases (97.8%) including all-layer positive in 36 cases (80%), and in all 72 OLD cases (100%) including all-layer positive in 63 cases (87.5%). When the CK17 positive rate was higher in OLD than in OLP and OLL, the all-layer positive rates in OLP and OLL both exceeded 75%. Thus, findings of CK17 immunostaining may not be useful to exclude OLD from OLP and OLL.

CAR is a transmembrane glycoprotein discovered as a viral adsorption site on epithelial cell surface. This molecule is expressed mainly on stratified squamous epithelial cells and gastrointestinal epithelial cells in adults, and is a component of the tight junction complex and one of the intercellular adhesion molecules. Study has suggested that the hexon protein of adenovirus particle binds to CAR on epithelial cell surface, and that integrin (an adhesion molecule) transmits signals intracellularly to regulate cell proliferation. The expression and function of CAR in colorectal and other cancers have been reported. CAR exhibits tumor suppressing function in human malignant tumors. Loss of CAR has been reported to attenuate intercellular adhesion in various cancer cells, promote cancer cell proliferation, and enhance invasion and metastasis. A possible explanation for these effects is that loss of CAR triggers epithelial-mesenchymal transition (EMT). In the present study, the rate of attenuation of CAR staining intensity was markedly higher in OLD (77.8%) compared to OLP (18.1%) and OLL (15.6%). This finding is useful for excluding OLD from OLP and OLL. Moreover, these findings also suggest the occurrence of EMT in OLD.

E-Cadherin is an epithelial marker. The expression of E-Cadherin has been reported to decrease when EMT occurs. In the present study, the rate of attenuation of E-Cadherin staining was markedly higher in OLD (89.2%) including all-layer positive in 72 cases (97.8%) and in 45 of 45 OLL cases (80.0%) including all-layer positive in 63 cases (75.9%), in 44 of 45 OLP cases (87.5%) including all-layer positive in 36 cases (80%). While the CK17 positive rate was higher in OLD than in OLP and OLL, the all-layer positive rates in OLP and OLL both exceeded 75%. Thus, findings of CAR immunostaining may not be useful to exclude OLD from OLP and OLL.

Ki-67 is a known cell proliferation marker. In normal epithelium, Ki-67 is expressed in the second row of the basal layer. In epithelial dysplasia, Ki-67 is expressed also in the first row of the basal layer and exhibits stacking expression from the basal/parabasal layer to the spinous layer. On the other hand, since OLP and OLL show liquefaction of the basement membrane, it is difficult to judge the presence or absence of Ki-67 expression in the first row of the basal layer. We therefore evaluated the stacking expression from the basal/parabasal layer to the spinous layer. In the present study, stacking expression of Ki-67 from the basal/parabasal layer to the spinous layer was observed in 7 of 83 OLP cases (8.4%) and in 6 of 45 OLL cases (13.3%). These low rates were similar to the normal mucosa. On the other hand, stacking expression of Ki-67 was observed in 22 of 72 OLD cases (30.6%), and this rate was higher compared to OLP and OLL. Thus, this finding is useful to some extent to differentiate OLP from OLD, and OLL from OLD.

Compared to epithelial dysplasia in general, the Ki-67 expression rate in the spinous layer was low in the present series. When Ki-67 expression is not observed in the spinous layer, differentiation of OLD from OLP or from OLL would be difficult. However, stacking expression of Ki-67 becomes more evident when the degree of dysplasia increases. Thus, this finding is useful to exclude OLD lesions with high potential of malignant transformation from a diagnosis of OLP or OLL.

Immunohistochemical expression of the cancer suppressor gene p53 reflects gene mutation and is being used as a marker for malignant transformation and prognosis. In healthy epithelium, p53 is expressed in cells of the basal/parabasal layer. In epithelial dysplasia, p53 expression from the basal layer to the spinous layer has been reported. In the present study, p53 expression from the basal layer to the spinous layer was not observed in OLP (0%), while the expression rate was higher in OLD (14 of 72 cases, 19.4%) than in OLL (2 of 45 cases, 4.4%). Thus, p53 immunostaining may be useful to some extent in differential diagnosis. However, compared with epithelial dysplasia in general, the p53 expression rate in the spinous layer is low in the present series. When p53 expression is not observed in the spinous layer, differentiation of OLD from OLP or from OLL would be difficult.

Malignant transformation was observed in 4 cases, all of which were OLD, while none of the OLP and OLL cases showed malignant transformation. Whether OLD is derived from healthy oral mucosal epithelium or from OLP or OLL is a subject of future study. Considering the usual neoplastic process of healthy epithelium transforming to epithelial dysplasia and subsequently developing into carcinoma in situ and further to squamous cell carcinoma, OLD should be considered as a lesion with the potential of malignant transformation. In this study, the 4 cases in which OLD developed into squamous cell carcinoma had moderate to severe epithelial dysplasia, indicating that severity of dysplasia may be associated with malignant transformation. Attenuation of staining intensity for CAR and E-Cadherin was observed in OLD, suggesting a possibility that reduced CAR expression may be involved in malignant transformation through weakening cell junctions and triggering EMT.

In conclusion, excluding OLD in the diagnosis of OLP and OLL is important for deciding treatment. A diagnosis of OLP or OLL is indicated when the lesion is CK13 positive and CK17 positive, with no attenuation of staining intensity for CAR and E-Cadherin from the basal layer to the lower one-third of the spinous layer. On the other hand, a diagnosis of OLD is indicated when the lesion is CK13 negative and CK17 positive, with attenuation of staining intensity for CAR and E-Cadherin from the basal layer to the lower one-third of the spinous layer. Furthermore, the present findings suggest that in OLD, reduced CAR expression may participate in malignant transformation by weakening cell junction in the epithelium and inducing EMT.

Acknowledgements
This study was supported in part by Research Promotion Grant (NDU Grants N-18005) from The Nippon Dental University. We are grateful to Ms. Michiko Moride for technical guidance.

Conflicts of Interest
The authors declare that they have no conflicts of interest with respect to the authorship or publication of this article.

References
1. Sugerman PB and Savage NW. Oral lichen planus causes, diagnosis and management. Aust Dent J 47: 290-297, 2002
2. Al-Hashimi I, Schiffter M, Lockhart PB, Brennan M, Migliorati CA,
Axéll T, Bruce AJ, Carpenter W, Eisenberg E, Epstein JB, Holmstrup P, Jontell M, Lozada-Nur F, Nair R, Silverman B, Thongprasom K, Thornhill M, Wannakulasuriya S and van der Waal I. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 103: e1-e12, 2007

3. van der Waal I. Oral lichen planus and oral lichenoid lesions: A critical appraisal with emphasis on the diagnostic aspects. Med Oral Patol Oral Cir Bucal 14: E310-314, 2009

4. Walton LJ, Macey MG, Thornhill MH and Farthing PM. Intra-epithelial subpopulations of T lymphocytes and Langerhans cells in oral lichen planus. J Oral Pathol Med 27: 116-123, 1998

5. Zhou XJ, Sugerman PB, Savage NW, Walsh LJ and Seymour GJ. Histopathology of the Skin, 11th ed, ed by Elder DE, Wolters Kluw -er Health, Philadelphia, 2015, pp 192-239.

6. Khan A, Farah CS, Savage NW, Walsh LJ, Harbrow DJ and Sugerman PB. Th1 cytokines in oral lichen planus. J Oral Pathol Med 32: 77-83, 2003

7. van der Meij EH, Scheepman K and van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: A prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 96: 164-171, 2003

8. Juntunen N, Mahajan S, Rao NN, George T and Boaz K. Histochemical analysis of pathological alterations in oral lichen planus and oral lichenoid lesions. J Oral Sci 48: 185-193, 2006

9. Krutchoff DJ and Eisenberg E. Lichenoid dysplasia; a distinct histopathologic entity. Oral Surg Oral Med Oral Pathol Oral Radiol 60: 308-315, 1985

10. Mobini N, Caire ST, Hu S and Kamino H. Lichen planus in noninfectious erythematous, papular, and squamous diseases. In: Lever’s Histopathology of the Skin, 11th ed, ed by Elder DE, Wolters Kluwer Health, Philadelphia, 2015, pp 192-239.

11. Ismail SB, Kumar SK and Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. J Oral Sci 49: 89-106, 2007

12. Scully C and Carrozzo M. Oral mucosal disease; lichen planus. J Maxillofac Surg 46: 15-21, 2008

13. Montebugnoli L, Venturi M, Gissi DB and Cervellati F. Clinical and clinicopathological features and malignant transformation of oral lichen planus: A 12-years retrospective study. Acta Odontol Scand 71: 834-840, 2013

14. Bardelli E, Amadori F, Flocchini P, Bonadeo S and Majorana A. Clinicopathological features and malignant transformation of oral lichen planus: a 12-years retrospective study. Acta Odontol Scand 71: 834-840, 2013

15. Shearston K, Fathah B, Tai S, Hove D and Farah CS. Oral lichenoid dysplasia and not oral lichen planus undergoes malignant transformation at high rates. J Oral Pathol Med 48: 538-545, 2019
gies, applications, and limitations. Lab Inves 52: 243-256, 1985
37. Moll R, Divo M and Langbein L. The human keratins: biology and pathology. Histochem Cell Biol 129: 705-733, 2008
38. Stecker K, Vieth M, Koschel A, Wiedenmann B, Rocken C and Anders M. Impact of the coxsackievirus and adenovirus receptor on the adenoma-carcinoma sequence of colon cancer. Br J Cancer 104: 1426-1433, 2011
39. Huang KC, Altinoz M, Wosik K, Larochelle N, Koty Z, Zhu L, Holland PC and Nalbantoglu J. Impact of the coxsackie and adenovirus receptor (CAR) on glioma cell growth and invasion: Requirement for the C-terminal domain. Int J Cancer 113: 738-745, 2005
40. Matsumoto K, Shariat SF, Ayala GE, Rauen KA and Lemer SP. Loss of coxsackie and adenovirus receptor expression is associated with features of aggressive bladder cancer. Urology 66: 441-446, 2005
41. Anders M, Vieth M, Röcken C, Ebert M, Pross M, Gretschel S, Schlag PM, Wiedenmann B, Kemmer W and Hörcker M. Loss of the coxsackie and adenovirus receptor contributes to gastric cancer progression. Br J Cancer 100: 352-359, 2009
42. Anders M, Rösch T, Küster K, Becker I, Höfler H, Stein HJ, Meininger A, Wiedenmann B and Sarbia M. Expression and function of the coxsackie and adenovirus receptor in Barrett's esophagus and associated neoplasia. Cancer Gene Ther 16: 508-515, 2009
43. Saito K, Sakaguchi M, Iioka H, Matsui M, Nakanishi H, Huh NH and Kondo E. Coxsackie and adenovirus receptor is a critical regulator for the survival and growth of oral squamous carcinoma cells. Oncogene 33: 1274-1286, 2014
44. Nohara F, Moride M and Katagiri M. A study on the relationship between apoptosis-associated factors and clinicopathological features in tongue squamous cell carcinoma. J Jpn Stomatol Soc 57: 25-37, 2008
45. Shailaja G, Kumar JV, Baghirath PV, Kumar U, Ashalata G and Krishna AB. Estimation of malignant transformation rate in cases of oral epithelial dysplasia and lichen planus using immunohistochemical expression of Ki-67, p53, BCL-2, and BAX markers. Dent Res J 12: 235-242, 2015
46. Regezi JA, Zarbo RJ, Regev E, Pisanty S, Silverman S and Gazit D. p53 protein expression in sequential biopsies of oral dysplasias and in situ carcinomas. J Oral Pathol Med 24: 18-22, 1995
47. Ogden GR, Kiddie RA, Lunny DP and Lane DP. Assessment of p53 protein expression in normal, benign, and malignant oral mucosa. J Pathol 166: 389-394, 1992
