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The Role Of Ki-67 In Oral Leukoplakia-Review Article.

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ABSTRACT

Leukoplakia is the most common oral precancerous lesion which might evolve into oral cancer. Apart from the usual histopathology which shows the degree of dysplasia there are no other reliable marker(s) which would depict which lesions will develop into oral cancer. So far, the role of Ki-67 in oral leukoplakia has been extensively investigated. Therefore, we searched Pubmed regarding the role of Ki-67 in oral leukoplakia in the last 25 years and 30 articles were retrieved. The results of this review suggest that Ki-67 seems to be very reliable immunohistochemical marker for malignant progression.

Keywords: Ki-67, leukoplakia, malignant potential, biomarker.

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INTRODUCTION

Prediction of the future behaviour of oral precancerous lesions such as oral leukopakia and oral lichen planus is unreliable in clinical practice.It is known that the grade of dysplasia is associated with malignant development, but as the only indicator it is not reliable. Abillity for malignant transformation in oral leukoplakia is unpredictable. Uptill now, there is no widely accepted specific biomarker for risk prediction of malignant transformation in oral premalignant lesions (1). Ki-67 has been widely investigated and most of the results suggested that it might be reliable predictor of malignant transformation. Location of Ki-67 and cell features are dynamic during the cell cycle, being low during the G1 phase and early S-phase, but it progressively increases during the mitosis. According to that, it seems that Ki-67 is an valuable biomarker of various phases of the cell growth (2). Ki-67 is an marker of nuclear proliferation which allows differences regarding proliferation between oral lichen planus, oral leukoplakia and oral cancer.It was previosuly suggested that there is a difference between Ki-67 expression in normal epithelium, precancerous lesions and oral cancer. He et al. (3) reported that Ki-67 expression varied between normal oral mucosa being 30%, oral leukoplakia (56.3%) and oral squamous cell carcinoma (79.2%). Furthermore, Lameira et al. (4) reported that Ki-67 expression was higher in oral cancer when compared to the mild and moderate dysplasia which was also confirmed by Teresa et al. (5), Liu and Klein-Szanto (6)as well as Soares et al. (7) and Santos-Garcia et al. (8).Kovesi and Szende (9) as well as Iamaroon et al. (10) and Nogami et al. (11) indicated that p53 and Ki-67 depict unfavourable prognosis in leukoplakia i.e. progression to oral cancer.Zhang et al. (12) investigated few markers regarding prediction of malignant transformation of leukoplakia and stated that Ki-67 among others also had significant impact.

MATERIALS, METHODS AND RESULTS

Pubmed was searched in order to find out articles published regarding the role of Ki-67 in patients with oral leukoplakia. Articles regarding proliferative verrucous leukoplakia and animal studies were excluded. Therefore, 30 papers were included.

DISCUSSION

In the most of the studies Ki-67 showed a good prognostic value in oral squamous cell cancer. Furthermore, its prognostic value in oral premalignant lesions proved to be good as well**.** Zoeller et al(13) investigated expression of Ki-67 in 80 biopsies of suspected oral dysplastic lesions and 40 oral squamous cell carcinomas. Results of this study showed that percentages of Ki-67 positive cells increased according to the histopathological degree of malignancy. Furthermore, correlation between the precentages of Ki-67 positive cells and cells in S-phase was detected. Liu et al. (6) searched the literature on immunohistochemical markers of cell proliferation in normal epithelium and oral leukoplakia. They found a very low proliferative activity in normal epithelium than in oral leukoplakias containing low grade dysplasia. Furthermore, high grade dysplasia could be differentiated from low grade dysplasia and normal epithelium by the presence of proliferating cells in the superficial cell stratum. These changes were detected with several markers including Ki-67. Similar results were presented in study of Tete at al. (14), which found weak expression of Ki-67 in normal mucosa, paraneoplastic lesions and in mild dysplasia, while strong expression was detected in sever dysplasia and in tumours.

Expression of p53 and Ki-67 increases when normal oral mucosa becomes dysplastic and undergoes malignant transformation (8). This was also confirmed in study which used computer-assisted analysis of cell proliferation markers in fibrous inflammatory hyperplasia (FIH), OL and OSCC. Expression of Ki-67 increased in the following order: FIH, OL and OSCC and these results indicate that Ki-67 is good marker for predicting proliferative activity in benign, premalignant and malignant lesions (5).

Furthermore, loss of p53 is in correlation with progression of premalignant to malignant lesions, as well as with increased Ki-67 with high tumor grade (15). Coexpression of Ki67 and p53 in correlation with an increase of degree of dysplasia may be used for identification of high-risk lesions (7, 9, 16, 17).

Furthermore, Goncalves et al. (18) reported that 15 oral leukoplakic lesions had severe dysplasia (18.7%) while 40 samples (50%) had combined high Ki-67/p53 expression. The same authors (18) concluded that oral leukoplakia has immune evasion potential which is not dependant upon cytological and

proliferation/apoptosis status.Bienk Dias et al**.** (19) found high expression of Ki-67 in dysplastic oral leukoplakia lesions (43.7%) as well as in non-dysplastc lesions (16,7%). As they investigated also survivin and p63 they concluded that all these leukoplakic lesions are potentially malignant, regardless of the histopathology.Mondal et al. (20) stated that 58.8% of their cases of oral leukoplakia exhibited a Ki-67 positivity of ≤ 5% and ≥25.8% exhibited it in the range of 6-25%. Only 15 (15.4%) patches were stained positively between 26% and 60%. Ki-67 labelling on a routine basis delivers the most convenient results for patients aged above 50 years, and/or addicted to tobacco products, and/or suffering from nonhomogenous patches.Öhman et al. (21) reported no significant differences in Ki-67 positive cells between oral leukoplakias that transformed into oral cancer and those which did not.Kumar et al(16) found out that the labelling index of Ki-67 were found to increase significantly with an increase of the grade of dysplasia within leukoplakia which was also confirmed by the study of Humayun and Prasad (22).. Statistical analysis of this study showed that precentage of p53 positive cells in healthy oral mucosa was 15-25% and increases up to 95% in malignant lesions. Different types of oral hyperkeratosis (without atypia, SIN1, SIN2 and SIN3) can be differentiated by Ki-67 and keratin 8, suggested Babichenko et al. (23) who also found the moderate positive correlation between proliferation and a keratin 8 expression in neoplastic epithelial cells.However, Sinanoglu et al. (24) found out that Ki-67 expression increased with the severity of lesions which defined different subgroups except there was no significant difference between the hyperkeratosis and oral intraepithelial neoplasia. Pigatti et al.(25) In their retrospective study data on 14 OLP and 14 OL (moderate and severe epithelial dysplasia) were immunohistochemically analysed and the results showed that most of the OL (64.3%) sections were stained positive for Ki-67 in more than 50% of cells.

Furthermore, Chandak et al. (26) reported significantly higher Ki-67 labeling index and actual proliferation index in OL with dysplasia compared to OL without dysplasia.

Except of p53, positive correlation with increased Ki-67 was found with filament – keratin 8 in different types of oral hyperkeratosis (with/without atypia) (23), as well as with integrin-beta 1 (27) and p27 (28). Some of the studies have demonstrated p75 neurotrophin receptor (p75NTR) as a useful marker of kertinocyte stem cells. This stem cell marker was used to identify cancer stem cells in various types of cancers, but it's expression have not been fully understood in OSCC and OL. Immunohistochemical expresion of p75NTR and Ki-67 was analyzed in 112 OL and 81 OSCC. Results of this study suggest increased expression of p75NTR in undifferentiated cell populations in OL and OSCC, and that p75NTR is involved in poor prognosis of OSCC (29). Alteration of combined biomarkers were proposed to define high risk OL . The combined p53/p16(INK4a)/Ki-67 alteration had showed a negative predictive value (NPV) and sensitivity of 100%, specificity of 97% and positive predictive value (PPV) of 67% unlike the combined p53/p16(INK4a)/Cyclin D1 alteration which had 97% NPV and sensitivity of 50%, specificity of 90% and only 25% PPV (30).

Zhang et al(12)developed nomogram for risk prediction of malignant transformation in OL using clinical data (age and degree of dysplasia) and combined biomarkers. Malignant transformed (n=22) and untransformed (n=138) OL samples with median follow-up period of 11.3 years were immunohistochemically stained. Results of this study showed that all biomarkers, including Ki-67, were proven to be significant for prediction of malignant transformation in OL. According to that, authors proposed a nomogram with prognostic factors for predicting the 5-, 10-, and 15- year progression free surival of OL.

In conclusion, although most of the studies emphasize prognostic significance of Ki-67 expression in oral premalignant lesions, further investigations are needed to confirm and validate these results.

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