GLOBAL GENE EXPRESSION PROFILE IN THE PROGRESSION OF ORAL PROLIFERATIVE VERRUCOUS LEUKOPLAKIA.

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BACKGROUND: Proliferative Verrucous Leukoplakia (PVL) is a distinct and aggressive form of leukoplakia. PVL has an unknown etiology, mainly affecting women over 50, with no clear association with HPV infection, tobacco and alcohol consumption. High rates of recurrence and malignant transformation are observed. Although several treatment options were proposed, none is fully effective. Currently, there are still no molecular markers for malignant progression of PVLs.

HYPOTHESIS: A global gene expression analysis can unveil transcript markers and disrupt biological pathways associated with tumor progression, which can be useful to comprehend the natural history of PVLs.

METHODS: Six patients were enrolled in the study, including three matched samples representing the progression model: leukoplakia (L), tumor (T), and normal adjacent (NA) tissues. RNA extraction was conducted using RecoverAll™ (Life) kit in formalin and paraffin-embedded (FFPE) samples. The GeneChip Human Transcriptome Array 2.0 (HTA) (Affymetrix) was used to evaluate gene expression analysis. The fluorescence signals were captured by the Affymetrix GeneChip Scanner 7000 and the analysis was performed using the Affymetrix Analysis Transcriptome Console (TAC) version 2.0. ANOVA-paired linear analysis was employed to compare the different tissues from each patient. Results were collectively interpreted using *in silico* molecular analysis (IPA, Ingenuity Systems and KOBAS v 2.0).

RESULTS: A linear progression model, ranging from histological normal to malignant neoplasia (NA *versus* L *versus* T), was used to study the expression profile of PVL (Fold Change ± 1.5 and $P<0.05$). Twenty-nine genes were observed as down-expressed (NA > L > T) and six as overexpressed (NA < L < T). Five altered canonical pathways were observed by IPA and KOBAS ($p <0.05$), most of them related to cellular adhesion and cytoskeleton. Furthermore, two main molecular networks revealed an inhibited state prediction of *ESR1* and *TP53*.

CONCLUSION: The results revealed putative transcripts markers and biological pathways of different stages of the PVL progression, which can be useful in the management of PVL patients in the future.