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Prevalence of Human Papillomavirus in Tissue Lesions of Oral Lichen Planus Patients

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ABSTRACT

Introduction:Oral lichen planus treatment offers favorable clinical results over time due to its widespread prevalence. However, to date, there is still no theoretical agreement on the cause of this disease. Therefore, the present study aimed to investigate the frequency of human papillomavirus (HPV) DNA in oral lichen planus (OLP) tissue samples by the polymerase chain reaction (PCR) method.

Methods: This retrospective study was carried out from 1387 to 1398 on 40 OLP samples (24non-erosive-atrophic and 16 erosive-atrophic forms) in the Oral Pathology Department of Mashhad Dental School. Polymerase chain reaction (PCR) was undertaken to identify HPV-DNA. Subsequently, the samples for HPV-DNA underwent PCR analysis again with the specific primers. The data were analyzed statistically by chi-square and independent t-test test regarding the significance level of lower than 0.05.

Results: The population consisted of 29 women (72.5%) and 11 men (27.5%) with an average age of 49.48± 2.78 years. Human papillomavirus DNA in none of the studied samples (in none of the groups) was detected by PCR. Gender distribution in the studied groups was not significantly different from each other, as the groups did not differ significantly in average age.

Conclusion: No HPV-positive samples were observed in oral lichen planus samples based on the recent findings in the current study of the Iranian population. Nevertheless, the patients' demographic data were not meaningfully associated. More sample sizes with a control group and a complete medical history should be recruited in further studies. Using complementary methods to approve the PCR method can help further studies to demonstrate accurate results.

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Introduction

Lichen planus is a chronic systemic mucocutaneous disease commonly found in the oral cavity (1). The prevalence of lichen planus in various populations is between 0.49% and 1.43%(2). Oral lichen planus (OLP) is the mucosal analog of cutaneous lichen planus, often appearing in 4-5th decades of life with an uncertain etiology(1). The population-based studies indicated that the dominant prevalence of OLP by sex was more for women than men in a 1.4:1 ratio(3). OLP can commonly affect the tongue, gums, and buccal and labial mucosa,

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with buccal mucosa being the most common site affected (4). All types of OLP can be classified into two groups: erosive-atrophic form, including erosive, atrophic, bullous, and mixed types; and non-erosive-atrophic form, including papular, reticular, plaque, and mixed types (5).

The World Health Organization (WHO) identifies most cancerous lesions, particularly oral squamous cell carcinoma (OSCC), as the result of some specific potentially malignant oral disease (PMOD), including oral lichen planus (6), so that this lesion occupies a prominent place as it is usually the first sign of disease with a malignant metastasis of about 0.5%(7,8).

Although the etiology is not fully understood, it is mainly known to be triggered by different factors, including stress, trauma, overworking, malnutrition, endocrine disorders, salivary gland disorders, and infection (9-11).

Studies have shown that the association between oral lichen planus and viral infections ranges from 27% to 65%, with a higher frequency of HPV 16 and 18 (12-14)**.** Human papillomavirus (HPV) is the most predominant viral disease of the reproductive tract and the most common sexually transmitted contamination (15).

"Globally, 570,000 cases per year in women and 60,000 cases in men are attributable to HPV, respectively, 8.6% and 0.8% of all cancers occurring worldwide" (WHO)(16). The results of studies on the effect of HPV infection on erosive OLP in follow-up studies are still controversial (17). Currently, hybridization tests of tissue samples and smears are the methods for detecting human papillomavirus DNA (18).

The polymerase chain reaction (PCR) is the most frequent and sensitive type, and the improvement of this technique has resulted in a reduction in the amount of time it takes to run the test (19). HPV can be detected in different epithelia with the help of the PCR method to characterize the virus type in the lesions by nucleotide sequencing(20). The reported prevalence of HPV in oral lichen planus is still at issue due to the heterogeneity of the study methodology, including different sample types, storage, and variable sensitivity of virus detection procedures (21).

In a study reported by V Panzarella et al. in 2017, patients underwent oral brushing, and HPV-DNA was searched by combining the INNO-LiPA HPV genotyping system and a PCR assay. None of the cytological samples collected resulted in HPV-positive (22).

However, some other studies using the PCR method to detect HPV infection reported a higher risk of HPV infection on OLP(23,24). Since high-risk HPV may play a pivotal role in the malignant transformation of lichen planus, little is known about the association due to different sample types and detection procedures. Also, considering the numerous controversies listed above(12,25), the authors aimed to investigate the prevalence of human papillomavirus DNA in oral lichen planus samples in Mashhad with PCR analysis.

Materials and Method

Study Design and Sample collection

This retrospective study was conducted on 40 paraffin blocks with a definite histopathological diagnosis of OLP based on "modified World Health Organization (WHO) criteria "(26). The study sample included 24 non-Erosive-Atrophic OLP and 16 Erosive-Atrophic OLP specimens of previously diagnosed oral lichen planus of people referred to the Oral pathology department, dental school, Mashhad University of Medical Sciences from 1387 to 1398. The Ethics Committee approved this study at Mashhad University (Code: IR.MUMS.DENTISTRY.REC.1398,015).

40 OLP-diagnosed paraffin blocks were checked to confirm the previous diagnosis, suitable fixation, and adequate amount of lesion to extract DNA, all of which met our inclusion criteria. Patients with a history of receiving the HPV vaccine or taking an antiviral drug were excluded from the study. Those samples with dysplasia were excluded too.

DNA Extraction and Primer Design

Each formalin-fixed and paraffin-embedded (FFPE) specimen was cut with a microtome device (Leitz 1512-Germany) under an immaculate condition. Each time, the blade was cleaned with alcohol and xylol and then cut into 5µm thick sections under the biological hood. Then sections were prepared, placed in a sterile micro-tube, and transferred to the central laboratory for DNA extraction. The blocks were first shaken with ethanol in the laboratory to remove paraffin and xylol well. The samples underwent cell lysis using a digestive buffer.

In the next stage, to identify the HPV in the paraffin samples, firstly, the DNA of the whole tissue was extracted using a Parstous tissue DNA extraction kit (Mashhad, Iran). After its confirmation with a NanoDrop, 2000 spectrophotometer with a wavelength of 230, 260, and 280 nanometers, polymerase chain reaction (PCR) was applied with the capacity to amplify the virus subtypes.

PCR and HPV Detection

After DNA extraction from the samples, as described in the previous section, PCR was

performed for each sample using the Iranian Gene Fanavar Institute kit and according to the manufacturer's instructions. The PCR was carried out in Veriti thermal cycler, consisting of one cycle for 3 minutes at 94°C for initial denaturation. After that, 35 cycles were carried out for 20 seconds at 94°C for denaturation, 40 seconds at 60°C for annealing, 40 seconds at 72°C for the extension, and one cycle for 7 minutes at 72°C for the final extension.

After determining the quality of the purified DNA with primers identifying the β-globin gene (PC03/PC04), some specific general primers were used for HPV gene amplification (GP6+/GP5+). After the PCR process, the DNA fragments were separated based on size. The product of the samples containing the relevant band was used as a pattern and re-proliferated, using HPV-amplifying primers to ensure the band accuracy.

The application of PCR and determination of the positive cases were confirmed with the 440bp band. Furthermore, the 250bp band indicates the excellent quality of the extracted DNA and the accuracy of the PCR test.

PCR enhanced products were analyzed on 2% (HPV) Agarose gel containing 0.5 g/mol of ethidium bromide and visualized under ultraviolet light.

Statistical Analysis

Descriptive Statistics was used to report demographic data and results. The data were analyzed using chi-square and independent t-tests at a $P<0.05$.

Results

Demographic findings

In this study, 40 samples (11 male, and 29 feIn this study, 40 samples (11 male, and 29 female) of oral lichen planus in the pathology archive of Mashhad Dental School were divided into two subgroups (Erosive-Atrophic and Non-Erosive-Atrophic) and examined for HPV DNA.

The mean age was 49.48 ±16.53 years (between 16 and 81 years). The age distribution of patients was almost normal. There was no significant difference between the groups regarding mean age and gender (P-value < 0.05). Demographic information of each group is provided in Table 1.

Table 1. Demographic information of Erosive-Atrophic and Non-Erosive-Atrophic groups

Variable		Erosive-Atrophic OLP (n=16)	Non-Erosive- Atrophic OLP
Age*	Average	51.06	48.42
	Standard Deviation	17.62	16.07
Gender**	Male	4(25%)	7(27.5%)
	Female	12(75%)	17(72.5%)

Independent t test (p-value =0.626 *
Chi-square test (p-value =0.772 **

Measuring the purity of the extracted DNA

The absorption ratio at wavelength 260/280 nm was 1.82 (expected value of 1.8), which indicates the purity of the sample. In addition, the absorption ratio at wavelength 260/230 was 1.97 (standard value between 2 to 2.2), which demonstrates the purity of nucleic acids and the absence of impurities such as EDTA, carbohydrates, and phenols. Furthermore, the presence of two bands in positive control samples and one band in negative control samples confirms the accuracy of our test.

HPV Detection

HPV-DNA was not found in any of the samples from any group. PCR product of HPV detection kit was performed on 2% agarose gel. As a result, a clear band was observed for all samples, indicating a negative test result and confirming the test accuracy. To re-evaluate the accuracy of the experiments, PCR was performed for all samples for the GAPDH gene, which is a housekeeping gene and is present in all cells. As a result, a sharp, clear band was observed, illustrating the optimal quality of DNA samples extracted.

Discussion

OLP is a chronic inflammatory mucocutaneous disease (27). OLP might happen due to a wide range of factors; however, the leading causes of this disease are still controversial (28). Different triggers, including HPV, have been reported (29).

Knowing the causes of OLP allows dentists to make informed decisions about treatment settings, risk factor modification, and alternative treatment options (30). In this regard, efforts to explore the correlation between HPV and OLP have mainly comprised epidemiological studies of various populations (31).

In a screening procedure for human papillomavirus in oral lichen planus lesions, we investigated the HPV-DNA in tissue specimens

with the PCR method.

The association between OLP and human papillomavirus is still controversial due to a high prevalence rate ranging between 15.4% and 42.6% (32, 33). Our findings indicating no presence of HPV-DNA might be comparable to the results of some other studies, which reported no substantial evidence to prove the association between HPV incidence rate and OLP (14,34).

Furthermore, no meaningful connection was found between population parameters in the groups. After showing a different prevalence rate of HPV in this lesion, many studies have been conducted (25,35).

A systematic review and meta-analysis reported the overall incidence of OLP as about 0.89% among the general population. The study also reported a higher prevalence of OLP among women than men, mainly affecting people over 40. Additionally, the prevalence is lower in Asian countries. Due to the high heterogeneity of the included studies, our results should be viewed with caution (3).

In the present study, we found no relationship between HPV prevalence and OLP lesions among the Iranian population, with 100% negative for HPV in tissue samples using the PCR method. As a result, no association was found between the virus and atrophic lichen planus. Our results might be comparable to the findings of other studies conducted by Arirachakaran et al. and Khovidhunkit et al., which demonstrated a low HPV prevalence of about 2.7% and 0% in fresh-frozen tissue biopsy samples with the PCR method, respectively (4,25).

There is great variation in HPV incidence ratio for oral lichen planus samples among geographically different populations (36). In the present study, Kent Young et al. and Miller et al. supported the finding of previous reports conducted in the USA on HPV prevalence in OLP tissue specimens. They demonstrated no specific relationship between HPV and 6 OLP samples using biotinylated double-stranded DNA probes by in-situ hybridization (37,38). In contrast, an Iranian cohort assessing the prevalence of high-risk HPV in tissue and saliva samples reported a high prevalence of 27% HPV-positive tissue samples compared with saliva specimens (39). On the other hand, a prospective European study using two different chair-side sampling methods reported a 15% and 6% HPV prevalence using the PCR method following the biopsy and the cytobrush sampling methods, respectively (40).

A meta-analysis shows a strong association between HPV and OLP lesions than controls (41). The higher odds ratio (OR) with a 4.9-fold increase in OLP was reported with erosive subtypes than non-erosive subtypes (41). In line with this finding, Szarka et al. reported that this prevalence was higher in the Erosive-atrophic group (23). Rupture of the squamocolumnar junction and facilitating viral access may be the reason behind this result (42).

The influence of sex on HPV's prevalence in OLP is still controversial (43, 44). In the current study, sex revealed no significant association. Also, the case-control study conducted by Razavi et al. in 2009 revealed no relationship between patients' sex and the presence of this virus in the samples (45). In contrast, Gillison et al. suggested that men had a significantly higher prevalence than women for any oral HPV infection (46).

Age was another demographic risk factor studied in this investigation. In line with our study, Szarka et al. in 2009, concluded that the age distribution is not different in any of the groups (23). Some other authors came to the same conclusion (47).

According to several studies, HPV genotypes play a distinct role in developing OLP(17). Xun Chen et al. and other authors revealed that the most common virus in lichen planus lesions is HPV-16,18, a high-risk type (48-50).

Several epidemiological studies have shown wide-ranging fluctuations in the prevalence of HPV in oral precancerous lesions due to a great deal of variation in experimental methods, different sample sites such as keratinized or non-keratinized sites, differences in selection criteria, and sample collections, including biopsies and superficial scrapes (23,50,51).

It should be noted that due to the low prevalence rate of HPV in this lesion and lack of patients history, we were not able to analyze the confounding factors, including alcohol, cigarette consumption, clinical types (red, white, mixed), Hepatitis C virus, Diabetes Mellitus, Therapy, and diet (52).

PCR is the most sensitive method in which a false-positive response is possible (53). Therefore, conclusions from studies used in this way should be made with caution. Our study used GP6 + / GP5 + primers, which are very sensitive even in samples with a low microbial load. These primers can detect very short sequences of virus DNA in fixed samples, leading to very high sensitivity. Even though DNA is broken into tiny pieces during the fixation process, these primers can still detect them (54).

In conclusion, no HPV-positive samples in this study were observed, so the analysis of the confounding factors, including the history of smoking, alcohol consumption, or betel nut

chewing habit, was not possible. Due to our small sample size, it is suggested that future studies be conducted with more specimens. In addition, a control group for comparison can be recruited. The impossibility of getting a complete history of the patients is the present study's limitation. Getting a complete history of patients about tobacco, alcohol, sexual behavior, and immunosuppressive drugs should be considered in future studies.

Using complementary methods to determine HPV subgroups and the PCR method can help further studies demonstrate accurate results. These findings support a targeted effort to reduce the prevalence of OLP patients. Hence, we propose that this analysis be modified with these restrictions.

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Competing interests

The authors have no conflict of interest to declare.

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