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CHANGES IN ANTIGEN-PRESENTING (LANGERHANS) CELLS OF ORAL MUCOSA IN PATIENTS WITH HPV INFECTION

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ABSTRACT — Despite the fact that HPV infection is widespread among the population around the world, more than 150 strains of HPV viruses are known. At the present stage it is still unclear, why HPV-associated oral papillomas in dental patients either spontaneously undergo involution or become malignant. We investigated the quantitative dynamics of Langerhans cells depending on localization in the structure of such papillomas: in the peripapillary space, in the tissue of the oral mucosa in the presence of HPV infection, without a clinical picture of papillomas and in healthy tissue. It has been established that with long-term existing papillomas, antigen presentation is disturbed, and Langerhans cells can be an indicator of papilloma malignancy.

KEYWORDS — HPV; HPV-associated oral epithelial dysplasia; epithelial dysplasia, oral mucosa, Langerhans cells, malignancy.

RELEVANCE

According to static data obtained by the European Institute of Oncology (EIO) for the period 2000-2010, out of 675 patients with confirmed HPV-positive status, 48.1% of patients were diagnosed with cancer of the oral cavity, pharyngeal cavity and oropharyngial region (1.8 %, 2.2%, 40.4%, respectively) [6]. It is known that the barrier function of the epithelium is provided by constant interactions between various specific and nonspecific cellular and humoral defense mechanisms, however, their role in the conditions of viral HPV contamination at the present stage has not been studied, the causes of single formations and papillomatosis are unknown [2]. It should be noted that sometimes, for unknown reasons, the combination of drug therapy with the removal of all existing neoplasms can have a temporary effect with a high risk of reappearance of papillomas, which requires further deeper studies of this problem [1]. The danger of most HPV infections is that they can be latent, most clinical lesions are benign, with the possibility of transformation into malignant neoplasms [5]. Today HPV is recognized as the cause of cancer of the larynx, oral cavity and other organs [7]. Subtypes 6 and 11 are low-risk and usually present with genital warts and low-grade precancerous lesions [3]. HPV subtypes 16 and 18 are at high risk and are responsible for high-grade intraepithelial lesions that progress to malignant neoplasms [8].

Analysis of the literature revealed the absence of criteria for predicting the development of papillomatosis in ROS and pathogenic processes that cause the destruction and malignancy of periodontal tissues, which indicates the high relevance of research conducted in this direction [4]. Despite the successes achieved, the role of epithelial cells in the transmission of signals to the local immune system has not been sufficiently studied, as well as the importance of dendritic cells as carriers of periodontal pathogens to distant parts of the body, namely, their role in metastatic infection, which determined the direction of our research.

The aim of the research was to study changes in the system of local immunity of the oral mucosa (MO) in patients infected with HPV in order to improve the methods of diagnosis, prevention and treatment of complications in dental prosthetics.

MATERIAL AND RESEARCH METHODS

The subjects of the study were patients requiring dental prosthetics after trauma and adentia of infectious etiology, who had HPV infection with LIH MO of various localization, confirmed by PCR diagnostics aimed at determining the strain and viral load on the body. Langerhans cells were detected according to the protocol of Dako (Denmark) by a highly specific method of immune histochemistry using Anti-Human Monoclonal Mouse CD68 antigen EBM11, Y1 / 82A, Y2 / 131, Ki-M6, clone KP1, isotype IgG1, kappa.

In cases when conservative treatment and laser point methods for removal of large papillomas, accompanied by clinical complaints, produced no effect, surgical removal of neoplasms was used. In cases with suspicion of malignancy of the formation, histological studies were prescribed to determine the benign quality of the samples. This study was conducted in accordance with the fundamental ethical principles of the Declaration of Helsinki, the GCP (Good Clinical Practice, Good Clinical Practice) Rules and approved by the Interdisciplinary Ethics Committee of the Far Eastern Federal University (Vladivostok, Russia).

RESEARCH RESULTS AND THEIR DISCUSSION

The mechanisms of HPV infection, its clinical manifestations, histological features and differential diagnosis of pathologies of the oral cavity associated with HPV have not been fully disclosed. In our studies, the locally affected HPV RR was characterized by flattening of the papillae, local thickening of the epithelium and the appearance of the stratum corneum in atypical places, not on the chewing surfaces of the RR, but in the areas of localization of papillomas protruding above the RR surface (Fig. 1).

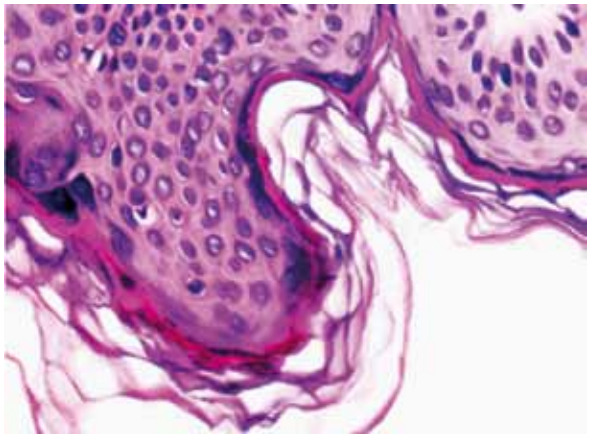

Fig. 1. *Papilloma tissue of HPV etiology in a 42-year-old patient. Staining with hematoxylin and eosin. Magnification ×100*

Langerhans cells (LC) are dendritic antigen-presenting cells present in the epithelium of the oral mucosa. Having studied quantitatively the density of Langerhans cells in the affected and intact epithelium using the method of immunohistochemical study, we did not find significant changes in the normal MO not affected by the virus, which indicated the absence of a primary defect in Langerhans cells. In contrast to the LIH MO data of the control group, the MO tissue in the structure of the papilloma in the layers of the epithelium contained an insignificant amount of Langerhans cells, and depending on the age of the presence of papillomas, Langerhans cells could be absent altogether, or single cells were identified (Fig. 2).

Studies of the number and localization of antigen-presenting cells in the HPV-infected oral mucosa (MO) epithelium showed that the percentage of Langerhans cells per 100 cells in the field of view in slices was significantly reduced in neoplasms, compared to the apparently clinically uninfected epithelium and surrounding papilloma tissue on the border with a healthy and unchanged oral mucosa (Table 1).

The morphological appearance of the identified Langerhans cells did not differ in the affected epithelial layers from intact samples of the oral mucosa. Langerhans cell activity is impaired in patients with papillomavirus dysplasia of oral mucosa, which can be partially explained by the interaction between viral-infected epithelial cells and inflammatory cells of the inflammatory infiltrate in the adjacent connective tissue lamina propria of loose connective tissue, which leads to inhibition of the response.

Migration, or death of Langerhans cells, their identification only in the connective tissue plate of the MO indicate a violation of antigen presentation in the COP structures, are evidence of a local defect of LIH MO and decrease in the barrier protective properties of the epithelium. For better informativeness of the dynamics of changes in the content of Langerhans cells in the MO of the control group and patients with HPV infection with clinical manifestations in the form of papillomas and without them, we presented the data in the form of a diagram in Fig. 3.

A noticeable decrease in the number of Langerhans cells per unit volume of the epithelium can be observed with HPV lesions of the epithelium, since it is possible that the virus is able to infect not only epithelial cells, but also Langerhans cells, like other mucosal cells. Thus, HPV infection may have both direct and indirect effects on LIH MO, affecting both cellular and humoral immunity.

CONCLUSION

The main elements of the classical LIH MO model in the age aspect, developed, supplemented and refined by V.E. Tolmachev. (2020) remain relevant today; however, our understanding of the dynamic interactions between various microbial and host factors has changed significantly. At the present stage, it has been established that the necessary conditions for the transition of chronic infection with human papillomavirus to carcinogenesis is the presence of high-risk HPV [7]. However, the distribution of genotypes

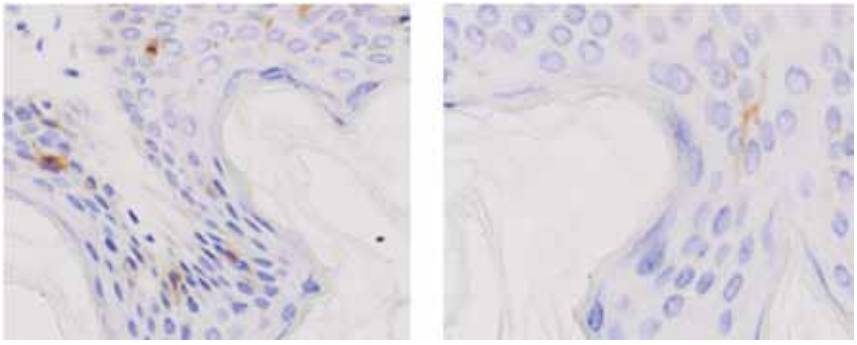

Fig. 2. Papilloma tissue of HPV etiology in a 42-year-old patient. Immunohistochemistry to identify the localization of Langerhans cells. a) an increase of 100; b) ×200

Table 1 Dynamics of the number of identified Langerhans cells depending on HPV infection in the oral mucosa В ТАБЛИЦЕ РУССКИЙ!!!!!!!!!!!!!!!!!!

Structures	Normal oral mucosa	СОР с ПВЧ		
		oral mucosa with HPV infection without papilloma	oral mucosa with HPV infection with papilloma	oral mucosa with HPV infection on the border with papilloma
Epithelium	4,10±0,023	1,1±0,07	0,52±	0,96±0,027
connective tissue plate of the oral mucosa	0	2,14±0,05	3,21±0,16	1,4±0,09

**P < 0,05*

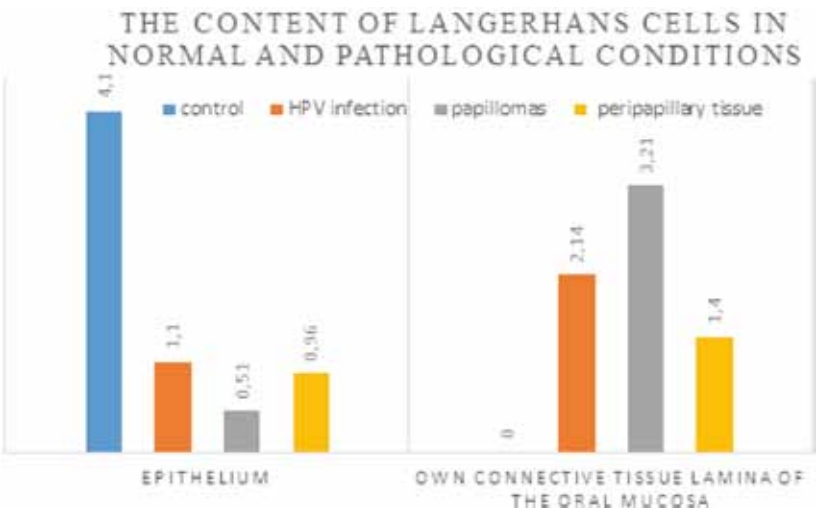

Fig. 3. Diagram of the dynamics of identification of Langerhans cells in health and disease with HPV etiology

shows that even low-risk HPV can cause MO cancer. The discrepancies in detection rates are likely due to the small sample size in the reviewed articles and different detection methods. Factors that may underestimate the prevalence of HPV include selectively searching for high-risk HPV, DNA destruction in fixed tissue, locally contaminated HPV, and possibly recovery from HPV infection before the time of biopsy. The dominant concept is that genetic and epigenetic changes in host cell genes are critical for the progression of precancerous lesions to invasive cancer. Although significant progress has been made in understanding the life cycle of HPV and its role in the development of malignant neoplasms, there is still an urgent need for precise surveillance strategies and targeted therapeutic options to eradicate this MO cancer in patients.

Given the prevalence of this viral infection and the strict type-specificity of currently available HPV vaccines, it is imperative to elucidate the molecular details of the natural course of HPV infection, as well as the biological activity of viral oncoproteins. To better understand the mechanisms involved in oncogenesis, it is necessary to deviate from dead-end ideas and develop new solutions and achieve an opportunity to justify effective therapeutic approaches to the prevention and treatment of malignant neoplasms associated with HPV. At malignancy, an increase in the activity of regulatory T cells leads to a decrease in the protective effect of the immune system against carcinogenesis. Under conditions of cancer, any increase in the activity of regulatory T

cells leads to a decrease in the damaging effect of the immune system on cancer cells.

FINDINGS

Systemic inflammatory processes and localized pathological processes mediated by the microbiome and LIH MO can be taken into account as diagnostic and prognostic biomonitors of malignancy of MO neoplasms.

An additional reduction in immunological surveillance at sites of potentially oncogenic human papillomavirus infection may increase the risk of malignant epithelial transformation.

LIH MO status can be identified based on histological characteristics and Langerhans cell count.

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