AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

UDC: 616.31-002.2:616.98:578.828.6:612.017.1

HPV-ASSOCIATED STOMATITIS: A LITERATURE REVIEW OF MORPHOLOGICAL AND IMMUNOHISTOCHEMICAL CHANGES

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Abstract. This literature review analyzes and synthesizes current data on the morphological and immunohistochemical features of the oral epithelium in HPV-associated stomatitis. While the role of the human papillomavirus (HPV) in oropharyngeal carcinogenesis is well-established, its significance in the development of benign and potentially malignant disorders of the oral mucosa, collectively referred to as "stomatitis," requires precise characterization. The review examines specific alterations in epithelial architecture and the expression patterns of key immunohistochemical markers, such as p16 and Ki-67, which are indicators of viral activity and disrupted cell proliferation. Based on the analysis of the literature, it is concluded that a combination of morphological and immunohistochemical methods is crucial for accurate diagnosis, assessment of progression potential, and developing management strategies for patients with HPV-associated oral mucosal lesions.
Keywords. HPV, Human Papillomavirus, Stomatitis, Oral Mucosa, Morphology, Immunohistochemistry, p16, Ki-67, Diagnosis, Review.

ВПЧ-АССОЦИИРОВАННЫЙ СТОМАТИТ: ЛИТЕРАТУРНЫЙ ОБЗОР МОРФОЛОГИЧЕСКИХ И ИММУНОГИСТОХИМИЧЕСКИХ ИЗМЕНЕНИЙ

Аннотация. Данный литературный обзор посвящен анализу и систематизации современных данных о морфологических и иммуногистохимических особенностях эпителия полости рта при ВПЧ-ассоциированном стоматите. Несмотря на то, что роль вируса папилломы человека (ВПЧ) в канцерогенезе ротоглотки хорошо изучена, его значение в развитии доброкачественных и предраковых поражений слизистой оболочки полости рта, объединяемых понятием «стоматит», требует четкой характеристики. В обзоре проанализированы специфические изменения архитектоники эпителия, а также паттерны экспрессии ключевых иммуногистохимических маркеров, таких как p16 и Ki-67, которые являются индикаторами вирусного воздействия и нарушения пролиферативной активности. На основе анализа литературных данных делается вывод о том, что комбинация морфологического и иммуногистохимического методов исследования является crucial для точной диагностики, определения потенциала прогрессии и разработки тактики ведения пациентов с ВПЧ-ассоциированными поражениями слизистой оболочки полости рта.
Ключевые слова. ВПЧ, вирус папилломы человека, стоматит, оральная слизистая, морфология, иммуногистохимия, p16, Ki-67, диагностика, обзор.

AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

HPV БИЛАН БОҒЛИҚ БЎЛГАН СТОМАТИТ: МОРФОЛОГИК ВА ИММУНОГИСТОКИМЁВИЙ ЎЗГАРИШЛАРГА ОИД АДАБИЁТЛАР ШАРХИ

Аннотация. Ушбу адабиётлар таҳлили HPV билан богланган стоматитда огиз эпителининг морфологик ва иммуногистохимиявий хусусиятлари тўғрисидаги долзарб маълумотларни таҳлил қилувчи ва умумлаштирувчидир. Одам папиллома вируси (HPV) нинг орофарингеал карциногенездаги роли яхши ўрганилган бўлса-да, "стоматит" деб юритиладиган, огиз шиллиқ қаватининг ёшимли ва зиёнли иллиги мумкин бўлган касалликлари ривожланишидаги аҳамияти аник тавсифлашни талаб қилади. Шунингдек, ушбу таҳлил эпителий архитектоникасининг ўзига хос ўзгаришлари, шунингдек, вирус фаоллиги ва ҳужайра кўпайишининг бузилиши курсаткичлари бўлган p16 ва Ki-67 каби асосий иммуногистохимиявий маркерларнинг ифодаланш ўзгачаликларини ўрганишга қаратилган. Адабиётлар таҳлили асосида, морфологик ва иммуногистохимиявий усулларнинг бирлашмаси HPV билан богланган огиз шиллиқ қавати лезиялари бўлган беморларни аник ташхислаш, прогрессияланиш имкониятини баҳолаш ва парвариш стратегияларини ишлаб чикиш учун мухим деган хулосага келинди.

Калит сўзлар. HPV, Одам папиллома вируси, Стоматит, Огиз шиллиқ қавати, Морфология, Иммуногистохимия, p16, Ki-67, Ташхис, Таҳлил.

Introduction. The human papillomavirus (HPV) is one of the most common sexually transmitted infections, with a proven tropism for epithelial tissues, including the oral mucosa [1]. According to the World Health Organization (WHO), up to 80% of sexually active individuals will be infected with HPV at some point in their lives, with the oropharyngeal region recognized as the second most frequent site of viral persistence after the anogenital tract [2]. While oncogenic HPV types (primarily 16, 18, 31, 33) are unequivocally associated with oropharyngeal squamous cell carcinoma, as reflected in the WHO Classification of Head and Neck Tumours [3], their role in the development of various benign and potentially malignant disorders of the oral mucosa requires closer scrutiny.

The term "HPV-associated stomatitis" in modern literature often implies a heterogeneous group of conditions, including benign proliferative lesions (squamous papilloma, focal epithelial hyperplasia, verruca vulgaris) and disorders with an uncertain malignant potential, such as HPV-associated multifocal leukoplakia [4, 5]. The clinical presentation of these conditions is often paucisymptomatic and non-specific: lesions can appear as whitish plaques, exophytic papillary growths, or flat erythemas, posing significant challenges for differential diagnosis with other inflammatory (e.g., candidal stomatitis, lichen planus) and reactive (e.g., fibroma, inflammatory papillary hyperplasia) processes [6].

The "gold standard" for diagnosis remains histological examination of a biopsy specimen. The classic morphological marker of HPV infection is koilocytosis – the appearance of cells with perinuclear halos, pyknotic, and hyperchromatic nuclei in the stratum spinosum [3]. However, the sensitivity and specificity of this feature vary. Koilocytes may be absent in the latent phase of infection or be weakly expressed, and similar changes are sometimes observed in other viral infections and reactive states [7]. This necessitates the use of more objective methods, among which immunohistochemistry (IHC) plays a leading role.

IHC allows for the visualization of the consequences of viral impact on the cell. Key markers in the diagnosis of HPV-associated lesions are the p16^{INK4a} protein and the Ki-67 proliferation antigen. The E6 and E7 oncoproteins of high-risk HPV types inactivate the tumor

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

suppressors p53 and pRb, respectively. The inactivation of pRb leads to compensatory overexpression of p16, making it a highly sensitive surrogate marker of transforming HPV infection [8]. In numerous studies on oropharyngeal cancer, diffuse, strong "block-type" p16 expression has become a reliable diagnostic and prognostic criterion [9]. In the context of benign oral mucosal lesions, the pattern of p16 expression requires more nuanced interpretation, as it can vary from focal to diffuse [10].

The proliferation marker Ki-67 is normally expressed only in the cells of the basal and parabasal layers of the epithelium. Under the influence of HPV, which disrupts cell cycle control, the proliferation zone expands, and positive nuclei are found in the middle and even upper thirds of the epithelial thickness [11]. Assessing the distribution of Ki-67 is crucial for differential diagnosis with dysplasia, which also features a loss of proliferative stratification but is typically accompanied by cytological atypia [12].

Thus, a comprehensive analysis combining classical morphology and immunohistochemistry allows not only for the verification of HPV etiology in stomatitis but also for an assessment of the lesion's biological potential, which directly influences patient management strategies. The aim of this literature review is to systematize and analyze current scientific data on the characteristic morphological and immunohistochemical (with a focus on p16 and Ki-67 markers) changes in the oral mucosa in HPV-associated stomatitis.

Materials and Methods. To conduct this review, a search of scientific publications was performed in the international databases PubMed, Scopus, Web of Science, and Google Scholar for the period 2005–2024. Search keywords and their combinations included: "HPV-associated stomatitis," "oral HPV," "p16 oral mucosa," "Ki-67 oral epithelium," "koilocytosis," "oral squamous papilloma," "focal epithelial hyperplasia." The inclusion criteria were original research articles, clinical case reports, meta-analyses, and review articles containing descriptions of histological and immunohistochemical characteristics of benign and potentially malignant oral mucosal lesions with confirmed HPV etiology (by PCR or in situ hybridization). A total of 52 relevant publications were selected for the final analysis.

Results:

1. Morphological Characteristics of HPV-Associated Oral Lesions

The conducted literature analysis revealed that HPV-associated lesions are characterized by a complex of histological changes varying with the clinical form.

Koilocytosis remains the most specific, though not absolutely sensitive, feature. A study by Singh et al. (2021) showed that koilocytes are detected in 70-80% of cases of PCR-verified HPV-positive papillomas and focal epithelial hyperplasia [13]. The variability in their detection is linked to the phases of the viral life cycle.

Acanthosis and Papillomatosis are observed in almost all cases of exophytic lesions (squamous papilloma). A review by Feller et al. (2019) emphasizes that the degree of papillomatosis can mimic benign papillomas of non-viral etiology, necessitating IHC for differentiation [5].

Para- and Hyperkeratosis often accompany lesions that clinically present as leukoplakia. In a paper by Woo (2022), it is indicated that in HPV-associated multifocal leukoplakia, parakeratosis can be unevenly expressed, alternating with areas of orthokeratosis [6].

Mitotic Figures in the upper layers of the epithelium, although not numerous, serve as an important additional sign indicating disrupted cell cycle regulation under viral influence [3].

AMERICAN ACADEMIC PUBLISHER
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2. Immunohistochemical Characteristics p16^{INK4a} Expression: Analysis of the data revealed a lack of uniformity in p16 expression patterns in benign lesions. A study by Lewis et al. (2020) reported strong, diffuse "block-type" positivity in only 25% of benign HPV-positive papillomas, while the remaining cases demonstrated focal or weak diffuse staining [10]. This contrasts with data on oropharyngeal cancer, where diffuse p16 expression is observed in >95% of cases [9]. The authors conclude that the intensity and extent of p16 expression appear to correlate with the oncogenic potential of the HPV type and the level of E6/E7 oncoprotein expression.

Ki-67 Expression: A systematic review by Fregonesi et al. (2022) demonstrated that HPV-associated lesions are characterized by an "expansion" of the proliferative pool. Unlike normal epithelium, where only basal and suprabasal cells are labeled, in HPV-stomatitis, Ki-67-positive nuclei are regularly found in the lower and middle third of the stratum spinosum [11]. However, unlike in dysplasia, proliferation rarely reaches the superficial layers, and the cells themselves lack signs of marked cytological atypia. The mean proliferation index (Ki-67 LI) in the group of benign HPV lesions in this study was 25-40%, which was significantly higher than in reactive papillomas (10-15%) but lower than in mild and moderate dysplasia (45-60%) [11].

3. Differential Diagnostic Aspects. The combination of morphology and IHC significantly improves diagnostic accuracy. Woo (2022) notes that the presence of koilocytosis, even in minimal amounts, combined with focal or diffuse p16 expression and an expanded, yet stratified, Ki-67 proliferation, highly suggests HPV-associated stomatitis [6]. In controversial cases, for instance, when differentiating from mild dysplasia, the key distinguishing feature is the absence of cellular and nuclear polymorphism, loss of cell orientation, and pathological mitoses in HPV-stomatitis, despite the increased proliferative activity [12].

Discussion

The presented literary analysis confirms that HPV-associated stomatitis represents a distinct pathomorphological entity. The central finding is the consistent presence of a specific immunohistochemical profile that complements the classical morphological signs. The diffuse "block-type" expression of p16, while not as frequent in benign lesions as in carcinomas, remains a highly valuable indicator of active high-risk HPV infection, serving as a reliable surrogate marker for E7 oncoprotein activity [8, 10]. Its interpretation, however, must be contextual, as focal positivity can also be seen in reactive and inflammatory conditions, albeit usually weaker. Equally important is the assessment of proliferative activity using Ki-67. The observed "upward expansion" of the proliferative compartment without significant cytological atypia is a hallmark of HPV's disruptive effect on cell cycle regulation, primarily through the degradation of pRb by E7 [11, 12]. This pattern is crucial for distinguishing HPV-associated lesions from true dysplasias, where disordered proliferation is coupled with significant nuclear pleomorphism and architectural distortion.

A significant challenge, as highlighted by the reviewed literature, is the clinical and histological overlap between HPV-associated lesions and other conditions, such as reactive papillomas or lichen planus [6, 7]. In these scenarios, the combination of morphology (searching for even focal koilocytosis) and a targeted IHC panel (p16 and Ki-67) becomes indispensable for a definitive diagnosis. The absence of a single pathognomonic feature underscores the necessity of a comprehensive diagnostic approach.

Future research should focus on standardizing the interpretation of p16 and Ki-67 staining patterns in benign oral HPV lesions and correlating these patterns with specific HPV genotypes

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
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and long-term clinical outcomes. This will help to better stratify the risk of malignant transformation in seemingly benign HPV-associated conditions.

Conclusions. HPV-associated stomatitis possesses a characteristic set of morphological features, the most significant of which is koilocytosis.
Immunohistochemical analysis using p16 and Ki-67 markers is an indispensable tool for confirming the diagnosis and assessing the biological potential of the lesion. A diffuse "block-type" p16 expression pattern combined with an expansion of the Ki-67 positive cell pool beyond the basal layer is a highly informative diagnostic pattern.
Establishing a final diagnosis requires a comprehensive assessment of histological and immunohistochemical data in conjunction with the clinical picture. Further research should be directed towards standardizing the evaluation of p16 and Ki-67 expression in benign HPV-associated oral lesions and elucidating the long-term risks associated with specific immunohistochemical profiles.

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