Human Papilloma Virus - Its Association with Epithelial Proliferative Lesions

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The Papillomaviruses are DNA viruses which belong to the Papova family, having a great affinity for epithelial tissue. They can produce proliferative lesions either in the skin or mucosa, in man and other animals. Various kinds of lesions, mainly benign, are caused by numerous types of HPV involving the well-known verruca vulgaris, oral papilloma, condiloma acuminatum and the focal epithelial hyperplasia, as well as a possible association with other alterations and lesions.

Key Words: human papilloma virus, papovavirus, papilloma, oral lesions.

Introduction

In general, the oral cavity has a basic structural composition, but each area has some particular aspect. We can observe alterations due to the action of irritative factors leading to a hyperkeratotic epithelium represented clinically by a white lesion. More complex alterations can be represented by erythematous or ulcerative areas presenting histologically severe epithelial aspects, caused by factors not yet well defined or even due to multiple agents. With this in mind, we can consider biological agents to be important factors causing local infections or different types of lesions of the oral mucosa. Among these biological agents, viruses are one of the most interesting because of their capacity to develop many types of diseases, their complexity and difficult therapeutical approach.

Many papillary, hyperplastic and verrucous lesions are associated with the human papilloma virus. Although this virus was one of the first to be related with neoplasias in man, it has not yet been possible to cultivate it in human tissues. This virus can cause proliferative lesions not only in humans, but also in other animal species. It can occur in man in various parts of the body, including the ano-genital region, larynx, nasal and oral cavity and other mucosae and also the skin (Syrjanen et al., 1989; Perrone and Premoli, 1992).

Papilloma virus is classified according to its sequence of nucleic acids, components of the genoma and the infected host. Its nomination is directly related to its natural host; the
virus which infects man is known as the human papilloma virus (HPV), and thus with other animals. It can be sub-classified in types when it is isolated from the same specie. When it presents less then 50% of nucleotides similar to other pre-existent viruses, it is designated as a new viral type, receiving a number according to the time of the discovery. If the homology is higher than 50% compared to other viruses already classified, then we have a sub-type and when the similarity of the nucleotides is near or even 100%, it is then considered to be a variety of the same viral type.

Until now, more than 70 types of HPV have been identified, many of them related to infections localized in specific areas of the human body (Syrjänen et al., 1989; Premoli-de-Pecoco et al., 1993; Van Heerden et al., 1993).

Viral reproduction occurs through its adherence to and penetration of a live cell and after its introduction into the intracellular medium, the virus looses its capsid. The viral genome entering the nuclei gains the capacity to code the cell structure and produces proteins which will give origin to the capsid, nucleic acid and the necessary enzymes to form a new virus intracellularly. They will then be free to infect other cells, and when cellular death does not occur, a chronic infection can probably succeed.

HPV infection

For a long time a varied and particular type of lesion in animals related to HPV in the mucosa and in the skin has been observed. This involvement of the mucosa and the skin is verified by many methods that detect the virus in the laboratory such as histopathological and ultrastructural (electron microscopy) analysis, immunohistochemistry, hybridization of viral DNA techniques and the recent polymerase chain reaction (PCR) (Green et al., 1986; Syrjänen, 1992; Van Heerden, 1993).

In humans, these lesions can be found in any part of the body, in the form of verruca vulgaris, condiloma acuminatum, papilloma, focal epithelial hyperplasia, and also observed in association with leukoplakia, fibrous hyperplasia, lichen planus and even carcinomas. Histological characteristics of the induction of HPV were found in verruca, condiloma and focal hyperplasia but not so evident in the papilloma. A possible correlation with carcinomas or pre-cancerous lesions based on histological aspects could not be verified (Garlick and Taichman, 1991).

The role of virus in immunosuppression, as can be observed in HIV patients, cannot be confirmed, but the frequencies of HIV-positive patients with some of these manifestations indicates that these individuals present a greater susceptibility to contamination or even reinfection of several types in uncommon regions of the body. Odontogenic lesions have not been studied in relation to HPV, and only some cases of ameloblastoma and odontogenic keratoctyst were related to HPV 6, 10 and 16 (Kellokoski et al., 1992; Van Heerden et al., 1993).

It is important to point out that in clinically healthy oral mucosa, Jalal et al. (1992) and Lawton et al. (1992) observed a 40-60% positivity for HPV type 16. Various types of
HPV can develop lesions with similar or specific clinical characteristics (Adler-Storthz et al., 1986a).

**Oral lesions**

*Condyloma acuminatum (Condylomata acuminata)*

This lesion is also called venereal wart represented by an infectious disease localized on the ano-genital region, involving sometimes the mouth and other warm moist areas of the body. It is a sexually transmitted disease caused by HPV 6 and 11 and clinically similar to other lesions of viral etiology. This lesion is uncommon in the mouth, but in young persons can be observed as soft, rose-colored, white or pink nodules, with a rough cauliflower-like surface. In general, asymptomatic, they can proliferate and coalesce to form sessile growths (Eversole et al., 1987; Adler-Storthz et al., 1986b). The incubation period is generally from one to three months, commonly occurring after oro-genital contact with previously infected partners (Abby et al., 1980).

Histologically, it is represented by the proliferation of a stratified squamous epithelium with papillary folds, parakeratosis, acanathosis and elongation of rete ridges. Koilocytic cells can be observed and have to be distinguished from other vacuolized cells (Abby et al., 1980; Eversole et al., 1987; Zeuss et al., 1991).

The most frequent sites of occurrence in the mouth are: tongue, lips and gingiva, infrequently affecting the mucosa lining, but any area of the mouth can be affected. The differential diagnosis comprises mainly the oral papilloma (squamous cell papilloma) and in some cases verrucous carcinoma.

Studies have shown that HPV types 6 and 11 are the most commonly associated with this lesion. Experimentally, the lesion can be induced by inoculation of viral particles in normal tissue of rats. The evidence of the participation of this type of virus is detected by electron microscopy, immunohistochemistry and hybridization of DNA (Sawyer et al., 1983; Eversole et al., 1987; Adler-Storthz et al., 1986b; Adler-Storthz, 1992; Syrjänen, 1992). The accuracy of the hybridization method is revealed by studies demonstrating that 100% positivity was observed in *condyloma acuminatum* for types 6 and 11 (Miller et al., 1991; Zeuss et al., 1991).

**Common wart (Vulgar wart of the mouth)**

This is another benign entity that is very common in the skin, especially in children, and is directly related to HPV. The occurrence of oral warts in the mouth is rare and presents similar clinical aspects to the papilloma. Infection occurs by direct contact between infected persons or by self-inoculation. If affects the lips more frequently and its clinical appearance is represented by an exophytic lesion, usually with a hyperkeratotic surface, forming finger projections and whitish appearance.
The main histological aspects are the degree of acantosis, vacuolization and the rete ridges at the margins, usually bending inward. According to the literature the involved types are 2 and 4 (in 55% of the oral cases), but also 6, 11 and 16 while the cutaneous type are types 1, 2, 4, 7 and 57 (Adler-Storthz et al., 1986a; Chang et al., 1991; Adler-Storthz, 1992; Van Heerden et al., 1993).

Oral squamous papilloma

This is the most common lesion related to HPV and is considered to be a benign neoplasm, occurring at any age, as an exofytic growth generally of small size and although it can occur anywhere in the mouth, the most frequent area is the soft palate, dorsum and lateral borders of the tongue and lower lip. Its surface is withish and presents a cauliflower aspect. Histologically the pattern of epithelial proliferation is repeated as in the previous lesions, with squamous cell acanthosis, hyperkeratosis and a centrally disposed fibrovascular core.

The HPV as the real etiology of the oral papilloma has been recently suggested, since in other animals it has been already well demonstrated. Viral particles, HPV antigens of the types 6 and 11, have been found in 80% of the lesions, while other researchers have found HPV antigens or DNA in 40-80% of the lesions studied. The similarity of oral papillomas and condylomas could be responsible for mistakes in the real frequency or prevalence of these lesions. In oral papillomas, the types detected were 6 and 11 but with different frequencies (Eversole et al., 1987; Syrjänen et al., 1989; Miller et al., 1991; Zeuss et al., 1991; Syrjänen, 1992).

Focal epithelial hyperplasia (Heck's disease)

This lesion is characterized clinically by asymptomatic, soft, multiple papules, mainly located on the lower lip, extending to the vermilion border. They are rare lesions prevalent in children or adolescents, with few cases occurring in adults. Historically, this disease has been described in Eskimos and North and South American Indians.

Histopathologically, the same pattern already described is seen but with more relevant cytologic changes such as koiocytosis, vacuolization, and mitosis, represented as nuclear degeneration. Papilloma virus particles and antigens can be found in these lesions, suggesting viral etiology. The types more frequently observed in the lesions were 13 and 32 (more than 90%). These types are not found in other lesions of the mouth or outside it, leading to the conclusion that they are exclusive to this disease (Sawyer et al., 1983; Garlick et al., 1989; Henke et al., 1989; Syrjänen, 1992; Van Heerden et al., 1993).

Discussion and Conclusions

Based on this review, we can appreciate how research has been developed in relation to HPV in the last ten years. The possibility of using new and more sensitive
techniques aids in the detection of the virus. With this improvement in methodology, new types have been discovered and more than 70 types of HPV have been already classified. We have to remember that this virus can be detected in various parts of the body, skin or mucosa, independent of an association with disease or lesion. It can also be detected in lesions as described with similar clinical and histological basic aspects despite the different types of virus associated.

Suggestions have been made of their possible causal relationship with oral leukoplakia, oral lichen planus, oral precancer and cancer. In relation to leukoplakia and lichen planus the literature point of view is that their etiologic role remains to be established, while in relation to precancerous lesions or cancer, the action of the virus and the role of all other factors which can synergistically act in its development is still questioned.

In relation to the proliferative lesions we can conclude that HPV is the etiologic agent of verruca vulgaris, focal epithelial hyperplasia, condiloma acuminatum and, with more recent proof, oral papilloma.

The possibility of other types still unknown seems to be true and future studies will offer more sensitive methods to detect them. The diversity of therapeutic approaches has to be mentioned here because they are different when dealing with skin or mucosa. In general, surgical treatment has been used in lesions of the mouth, but every case has to be well evaluated, remembering the different evolution, for example, of an oral papilloma and of a papilloma of larynx of bladder. The oral surgeon has to consider the different behavior of these lesions in different parts of the body, even when the etiologic agent is the same.

References


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