Clinical Oral Implications of Human Papillomavirus

Authored by Herb Bader, DDS

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Clinical Oral Implications of Human Papillomavirus

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LEARNING OBJECTIVES
After participating in this CE activity, the individual will learn:
• The clinical presentations of various human papillomavirus (HPV)-related oral lesions and their associated HPV genotypes.
• Contemporary adjunctive technologies for oral cancer screening.

ABOUT THE AUTHOR
Dr. Bader is a graduate of New York University Dental School and Harvard School of Dental Medicine postdoctoral program in periodontology. He is a Fellow of both the American and International Colleges of Dentistry and Omicron Kappa Upsilon and is also a Diplomate of the American Academy of Osseointegration. He holds the position of lecturer in periodontology at the Harvard School of Dental Medicine and is widely published in the literature in both refereed and nonrefereed journals. As an actively practicing periodontist, he maintains busy practices in Plymouth and Cape Cod, Mass. He is widely recognized as a leader in dental education and has been one of Dentistry Today’s Leaders in Continuing Education since 2007. He has lectured throughout the United States and Canada for a number of years on the subjects of inflammatory suppression, diagnosis, and adjunctive oral cancer screening and is now very much involved with the development of salivary diagnostics as a key to management of the periodontal patient. He can be reached at (339) 364-1402 or via e-mail at the following address: redabsr@aol.com.

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INTRODUCTION
The family of human papillomavirus (HPV) is the cause of the most globally widespread group of infections in humans, encompassing simple benign growths of soft tissue to highly malignant cancers. Genotypes of this family constitute the world’s most common sexually transmitted diseases (STDs). Many lesions seen in the oral cavity are caused by HPV. This article illustrates and discusses the clinical presentations of various HPV-related oral lesions, along with certain contemporary adjunctive technologies for oral cancer screening.

HPV is an epitheliotrophic DNA virus and has a number of implications in the oral cavity, covering the spectrum from an assortment of benign lesions to oral squamous cell carcinoma (OSCC). It is one of the most globally distributed viruses known, resulting in skin and mucosal lesions. The more than 120 genotypes of this family of viruses are the cause of the most widespread infections internationally. Variations in genotype in the DNA base-sequences of E6 and E7 allow differentiation into low-, intermediate-, and high-risk types. Table 1 illustrates the different oral disease types associated with various HPV genotypes.1-3

It is generally accepted that the carcinogenesis of OSCC is due to the accumulation of genetic alterations associated with malignant transformation of the oral epithelium.4 Oral premalignant lesions (OPLs) are generally asymptomatic lesions associated with varying degrees of conversion to malignancy. They are characterized by cellular dysplasia (literally meaning “disordered growth”), and infection by HPV. The genotypes associated with the lesions are seen in Table 1.

COMMON PREMALIGNANT LESIONS
Probably the most common OPL (also referred to in the literature as potentially malignant mucosal disease or oral potentially malignant disorder) is the white lesion, leukoplakia (Figure 1), presenting as a white plaque on the mucosa or gingival epithelium. The rate of progression of leukoplakias to malignancy has been reported to be 0.13% to 36.4%5 with worldwide prevalence estimated at 2.0%.6 The increase in cellular dysplasia leading to malignancy ranges between 1.0% and 17.5% per year.7 Treatment of this entity is excision
or simple continued observation, depending on the amount of
dysplasia. Removal of the lesion can be done via scalpel or
laser therapy. In some cases, removal of risk factors, such as
biting the tissue, can result in regression. The most common
risk factors for progression to OSCC are: males; long duration;
irregular, nonhomogeneous appearance; location on tongue,
floor of mouth, or soft palate; size greater than 200 mm; and
containing dysplastic cells. Subsequent studies have shown
that surgical removal of the lesion reduces risk for malignant
transformation, but is not 100% successful in complete risk
reduction. There is considerable evidence that HPV
genotypes 2, 6, 11, 16, and 18 can be demonstrated in more
than 50% of benign leukoplakias. The presence of the
high-risk genotypes 16 and 18 may have significant
prognostic implication for conversion to malignancy.

Erythroplakia and erythroleukoplakia are red and
red/white lesions whose differentiation from leukoplakia can
be made clinically by exclusion of other mucosal diseases
(Figures 2 and 3). The outstanding features of these lesions
are the bright red patches, and in combined lesions, the
white plaques. Early detection of leukoplakias can be aided
by available techniques for chemiluminescence or
autofluorescence with low specificity instruments. Tolamine
chloride (Toluidine Blue [Zila, a division of DenMat]) can be
used to detect dysplasia because of the dye’s affinity for
nuclear staining, enhanced by increased nuclear size in
dysplasia. The most definitive method to determine the
degree of dysplasia and subsequent transformation to
malignancy is the biopsy. The architectural changes
associated with dysplasia can then be visualized. There are
criteria established for identification which include change in
nuclear size and shape, cell size, and increased nuclear/cytoplasmic ratio. Cellular dysplasia is evidenced in
virtually all erythroplakias, and in 1.0% to 30% of
leukoplakias. A better measure of possible malignant
transformation may be evidence of abnormal DNA content
as in aneuploidy (ploidy referring to the number of single
sets of chromosomes in a cell). The determination of DNA
ploidy appears to be more predictive than dysplasia
histology. Ploidy status (aneuploidy: abnormal number of
chromosomes) and dysplasia are both predictive of
transformation, and can identify high-risk sites that are
normal clinically. This suggests that both ploidy status and
dysplasia may be used to determine risk in OPLs. It has
been suggested that detection of nondiploid cells using
brush biopsies can be useful in early detection of the
premalignant cells, as is DNA image cytometry of aneuploid
dysplastic lesions.

The loss of genomic material in one of a pair of
chromosomes is defined as loss of heterozygosity (LOH).
Studies have linked LOH as an early predictor of malignant
transformation. A number of studies have shown a positive
correlation between LOH and progression of cellular
changes leading to malignancy. It has been
demonstrated that determining LOH in clinically normal
mucosa was significantly effective in detecting pre-
malignancy. The p16 is a cyclin-dependent kinase
inhibitor protein which has been shown to consistently be
overproduced or expressed in SCC, and in other
nonmalignant oral lesions. It is currently the subject of
investigation as an acceptable surrogate and screening
marker for HPV oral lesions.

As noted in Table 1, there are other lesions of the oral
mucosa that are associated with HPV. The benign lesions
include squamous cell papilloma, verruca vulgaris,
condyloma acuminatum, and focal epithelial hyperplasia. While the specific etiological role of HPV is still being investigated, koilocytosis (a condition of cells characterized by perinuclear vacuolization) is the common histopathological effect amongst these lesions. \(^{22}\)

Table 2\(^{23}\) shows the topography of the oral cavity and the sites most likely to be infected with HPV. Note that the tongue, floor of the mouth, labial mucosa, and the posterior regions are the areas most involved. The study from which this topographical illustration was obtained points out the role of topography in HPV associated lesions. Figure 4 is a classical clinical presentation of leukoplakia in the floor of the mouth, which upon biopsy and DNA determination showed the presence of severe dysplasia and HPV-16.

Two more common lesions associated with a benign HPV genotype are squamous papillomas and verruca vulgaris (wart). They may be similar in appearance, and diagnosis is established by biopsy. Squamous papillomas are usually solitary, exophytic, and sometimes pedunculated. They have a roughened appearance and may present anywhere on the oral mucosa. Oral verruca has a similar appearance, with conspicuous hyperkeratinization. It too can be found on the oral mucosa and the vermilion border of the lip (Figures 5 to 7).

Focal epithelial hyperplasia (Heck’s disease) presents as discrete, small papillary lesions; although not observed very often, they are increasingly seen in HIV-positive patients. Another lesion, condyloma acuminatum, is a large wart-like growth usually seen in the genital area but can be found on the labial mucosa on occasion. It is a common STD.

**Screening, Examination, and Identification**

The importance of definitive recognition and treatment of oral lesions cannot be overemphasized. Knowing the relationship of HPV infection with many lesions, the possibility of transformation into neoplasia must be taken into consideration. The conversion of common leukoplakia into OSCC has been reported at 16% to 62\(^{24}\). The earlier the lesions are recognized and defined as to the level of dysplasia, the better the prognosis for the patient. Unfortunately, OSCC is usually diagnosed at its later stages, hence the relatively poor 5-year survival rate.\(^{25,26}\)

The following protocol is adapted from the standardized method recommended by the World Health Organization, and is consistent with protocols followed by the Centers for Disease Control and Prevention and the National Institutes of Health.

The sequence of evaluation begins as the patient enters the operatory and is seated, with the clinician noting the gait,
facial asymmetries, etc. Any changes on the skin such as fissuring, crusts, and/or color change are all noted. This is followed by a complete history prior to the physical examination. An essential part of the history relates to habits such as smoking, and discussion of anything that goes into the mouth, including smokeless tobacco, pipes, etc. History of previous lesions and/or oral disease is taken. Level of alcohol use is important, as well. The extraoral assessment as noted above is completed prior to palpation.

Regional lymph nodes are palpated bilaterally starting at the preauricular and moving back to the posterior cervical areas. The perioral and intraoral examination follows. First observed are the lips, labial and buccal mucosa, and gingivae, followed by an exam of the lingual and palatal aspects. The tongue examination begins with observation of the dorsum while at rest. Observe the protrusive movement, grasp the tip of the tongue with gauze, and examine the lateral borders, ventral surface, and floor of the mouth. Examine all hard and soft palate and oropharyngeal tissues, along with bimanual palpation of the floor of the mouth. Because of the prevalence of HPV-related changes, observation of the posterior oral cavity with particular attention to the soft palate, retromolar areas, and as far down the oropharynx as possible is important. The entire examination should take no more than 5 minutes.

**Adjunctive Screening Techniques**

Adjunctive screening techniques are currently available to help visualize occult and early lesions more definitively. The use of different wavelengths of light to stimulate reflectance as with the chemiluminescent Visilite+ unit (Zila, a division of DenMat), and the combinations of white, violet, and amber lights as with the Identafi (DentalEZ) depend on the altered state of tissues for visualization. In the case of Visilite+, suspected areas may be stained with the proprietary dye Toluidine blue (tolamine chloride) for more precise delineation. Another screening device is the VELscope (DenMat). This device, which can be fitted with a camera for record keeping, uses the excitation of fluorophores in the tissues to produce fluorescence which is altered in the presence of inflammation. A major value of these technologies lies in forcing the examiner to be more aware of deviations from the normal when screening patients.

A relatively recent addition to the armamentarium for early recognition is a salivary test for the presence of HPV in the oral cavity. This is a test called OraRisk (OralDNA Labs, a division of Access-Genetics), which is available as an important addition to screening for HPV. The test is very sensitive and specific for HPV 16, 18, and 32 along with other oncogenes of high, medium, and low risk. The HPV virus is somewhat unique in that it adheres to the mucosa at the point of contact, hence the aspect of sexual transmission. The presence of the virus does not mean the patient has OSCC, but is at increased risk for its development. In fact, the immune system can often clear the virus within a year. However, presence of HPV is an important guide toward increased and more frequent evaluation of the patient.

The significantly increased interest in HPV in light of the increasing incidence of SCC, especially in young people, has led to vaccines against HPV for both men and women, as well as a new technique for HPV detection in the cervical tissues, as an adjunct to the Pap smear. There is as yet no information on the validity for the vaccine against oral HPV. The dental profession's interest, of course, is oral HPV, but it is essential to have an awareness of the other ramifications of this entity because of its prevalence worldwide.

It must be emphasized that the definitive diagnostic technique for determining if a lesion is dysplastic or malignant is the biopsy. No patient has ever complained about a negative biopsy, but many lives have been saved by the procedure. The 5-year survival rate for those with localized OSCC is 83%, as compared with 36% for those whose disease has metastasized.

**CONCLUSION**

There are more than 120 genotypes of the HPV, and this family of viruses, which is sexually transmitted, is associated with a number of lesions in the oral cavity as well as elsewhere in the body. These lesions range from benign to highly malignant, including OSCC. Detection of oral lesions using current examination protocols in conjunction with certain adjunctive detection technologies is an important part of clinical dentistry. When lesions are detected, biopsy is the definitive diagnostic methodology to determine if a lesion is benign, dysplastic, or malignant.
REFERENCES

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POST EXAMINATION QUESTIONS

1. How many genotypes are there in the family of HPV?
   a. 60.
   b. 90.
   c. 110.
   d. 120+.

2. The family of HPV is the cause of the most globally widespread group of infections in humans.
   a. True.
   b. False.

3. Probably the most common oral premalignant lesion (OPL) is:
   a. Erythroplakia.
   b. Erythroleukoplakia.
   c. Leukoplakia.
   d. Verucca vulgaris.

4. The presence of the following high risk HPV genotype(s) may have significant prognostic implication for a lesion’s conversion to malignancy:
   a. 6 and 11.
   b. 30.
   c. 57.
   d. 16 and 18.

5. OPLs are generally asymptomatic. They are characterized by cellular dysplasia and infection by HPV.
   a. The first statement is true, the second is false.
   b. The first statement is false, the second is true.
   c. Both statements are true.
   d. Both statements are false.

6. The most definitive method to determine a lesion’s degree of dysplasia and subsequent transformation to malignancy is:
   a. Chemiluminescence.
   b. Salivary test for presence of HPV.
   c. Biopsy.
   d. Toluidine blue stain.
7. Ploidy refers to the number of single sets of chromosomes in a cell. Both ploidy status and dysplasia may be used to determine risk in OPLs.
   a. The first statement is true, the second is false.
   b. The first statement is false, the second is true.
   c. Both statements are true.
   d. Both statements are false.

8. The loss of genomic material in one of a pair of chromosomes is defined as loss of heterozygosity (LOH). There is no evidence that LOH is an early predictor of malignant transformation of a lesion.
   a. The first statement is true, the second is false.
   b. The first statement is false, the second is true.
   c. Both statements are true.
   d. Both statements are false.

9. The following oral lesion(s) is/are associated with HPV:
   a. Squamous cell papilloma.
   b. Verruca vulgaris.
   c. Condyloma acuminatum.
   d. All of the above.

10. The 5-year survival rate for those with localized oral squamous cell carcinoma is:
   a. 36%.
   b. 55%.
   c. 70%.
   d. 83%.
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6. ☐ a ☐ b ☐ c ☐ d

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