

Oral Verrucopapillary Lesions: A Diagnostic Conundrum

Lavanya A¹, Sowmya SV², Roopa S Rao³, Dominic Augustine⁴, Vanishri C Haragannavar⁵

ABSTRACT

Aim: This review provides an overview of various classifications and aims to focus on the characteristic distinguishing features of oral verrucopapillary lesions that direct towards arriving at a diagnosis and assessment of their biologic behavior.

Background: A variety of pathological conditions affect the normal morphologic and surface characteristics of the oral mucosa. Verrucopapillary lesions (VPLs) are one such group of diseases that are diagnostically disputed and comprise of a spectrum of reactive, benign and malignant lesions. They can be categorized broadly into focal and multifocal lesions.

Review results: The classic clinical, histopathological and Immunohistochemical characteristics of oral verrucopapillary lesions may help in their accurate diagnosis.

Clinical significance: Despite, few indistinguishable clinical presentations of VPLs, their specific morphology, etiology, and discrete histopathological features may ease out the diagnostic dilemma and facilitate appropriate treatment.

Keywords: Biologic behavior, Oral cavity, Verrucopapillary.

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INTRODUCTION

Benign, potentially malignant and malignant disorders of the oral cavity affect the normal morphology and stability of the mucosa manifesting as surface alterations. Such alterations can be appreciated as ulcerative, vesicubullous or papillary/ papular/ polypoid lesions.^{1,2}

Verrucopapillary lesions (VPLs) present themselves in varied clinical forms as papillary lesions exhibiting pointed or blunt finger-like projections, papular lesions featuring small sessile elevations and polypoid lesions with larger, pedunculated, exophytic growths that share similar histopathological features with subtle differences leading to diagnostic dilemma.^{1,2} Some normal oral mucosal structures present on the dorsum of the tongue, may share microscopic appearances similar to verrucopapillary lesions. Filiform, fungiform and circumvallate papillae are such structures showing parakeratinized surface projections microscopically.³ But, their diagnosis is of paramount importance as they include a wide spectrum of lesions that range from normal, benign, potentially malignant to malignant which drastically affect the treatment perspective. Hence, this review focuses on the characteristic

¹⁻⁵Department of Oral Pathology and Microbiology, Faculty of Dental Sciences, MS Ramaiah University of Applied Sciences, Bengaluru, Karnataka, India

Corresponding Author: Lavanya A, Department of Oral Pathology and Microbiology, Faculty of Dental Sciences, MS Ramaiah University of Applied Sciences, Bengaluru, Karnataka, India, e-mail: drlavmsdop92@gmail.com

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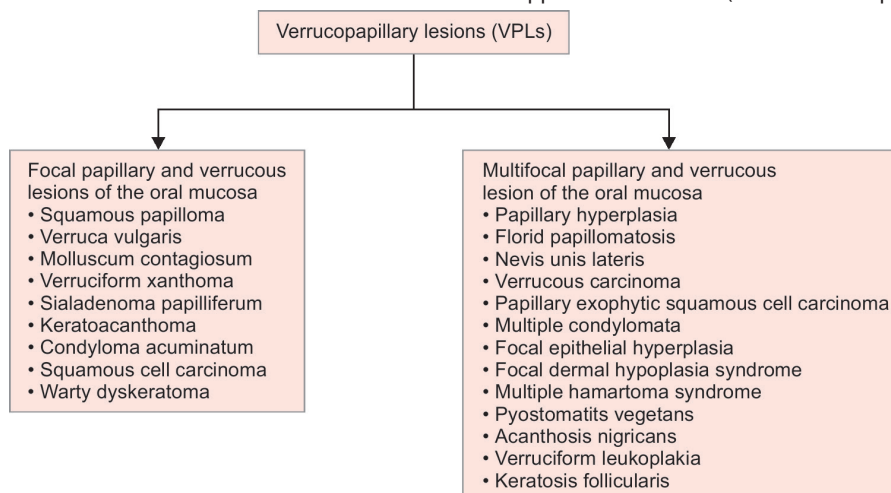
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features of oral VPLs that provide direction in their diagnosis and assessment of their biologic nature.¹⁻³

Classification

- Based on the number and appearance of the lesion (Eversole and Papanicolaou in 1983)¹ (Flow chart 1).

Flow chart 1: Classification of VPLs based on the number and appearance of lesions (Eversole and Papanicolaou, 1983)



- Based on the involvement of HPV as an etiologic factor (Eversole in 2000)¹ (Flow chart 2).
- Based on the type of the lesion (Regezi et al. 2003)³ (Flow chart 3)
- Based on malignant potential of the lesion (Thomas and Barret 2009)¹ (Flow chart 4)
- Based on the growth pattern (working classification) (Flow chart 5)

lesions—verrucous carcinoma, papillary exophytic squamous cell carcinoma, focal epithelial hyperplasia, verruciform leukoplakia.¹

Differential Diagnosis

In this section, an attempt has been made to discuss some of the common VPLs that have oral manifestations and a wide range of differential diagnosis on the basis of involvement of the lesion.

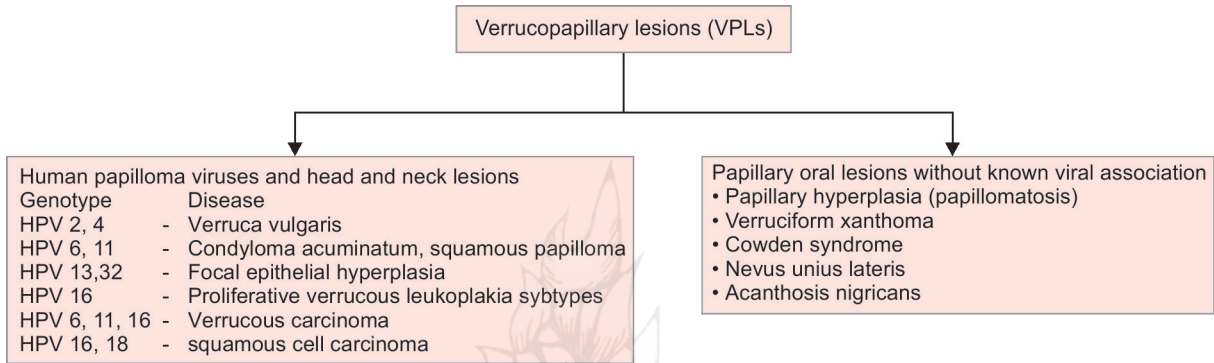
Verrucopapillary Lesions (VPLs) of the Oral Cavity

The commonly presenting oral verrucopapillary lesions may be broadly categorized into two groups, focal-squamous papilloma, verruca vulgaris, verruciform xanthoma, keratoacanthoma, warty dyskeratosis, and squamous cell carcinoma and multifocal

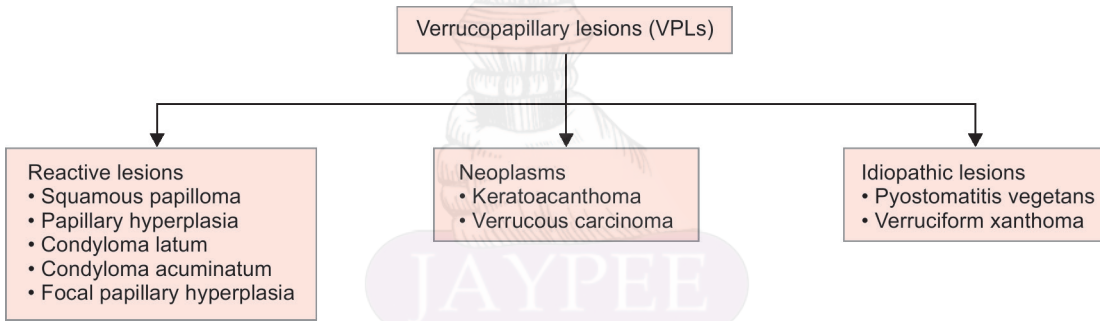
Focal Papillary Lesions

Localized papillary growths are depicted by non-viral and viral epithelial proliferations that may be sessile or pedunculated. These lesions show normal coloring while others are white along with

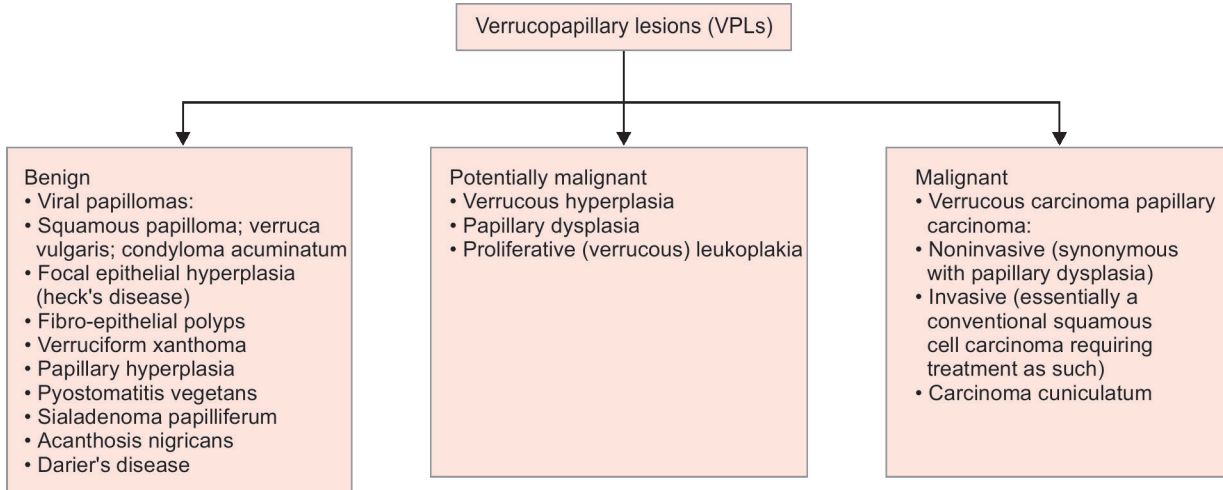
Flow chart 2: Classification of VPLs based on the involvement of HPV as an etiological factor (Eversole, 2000)



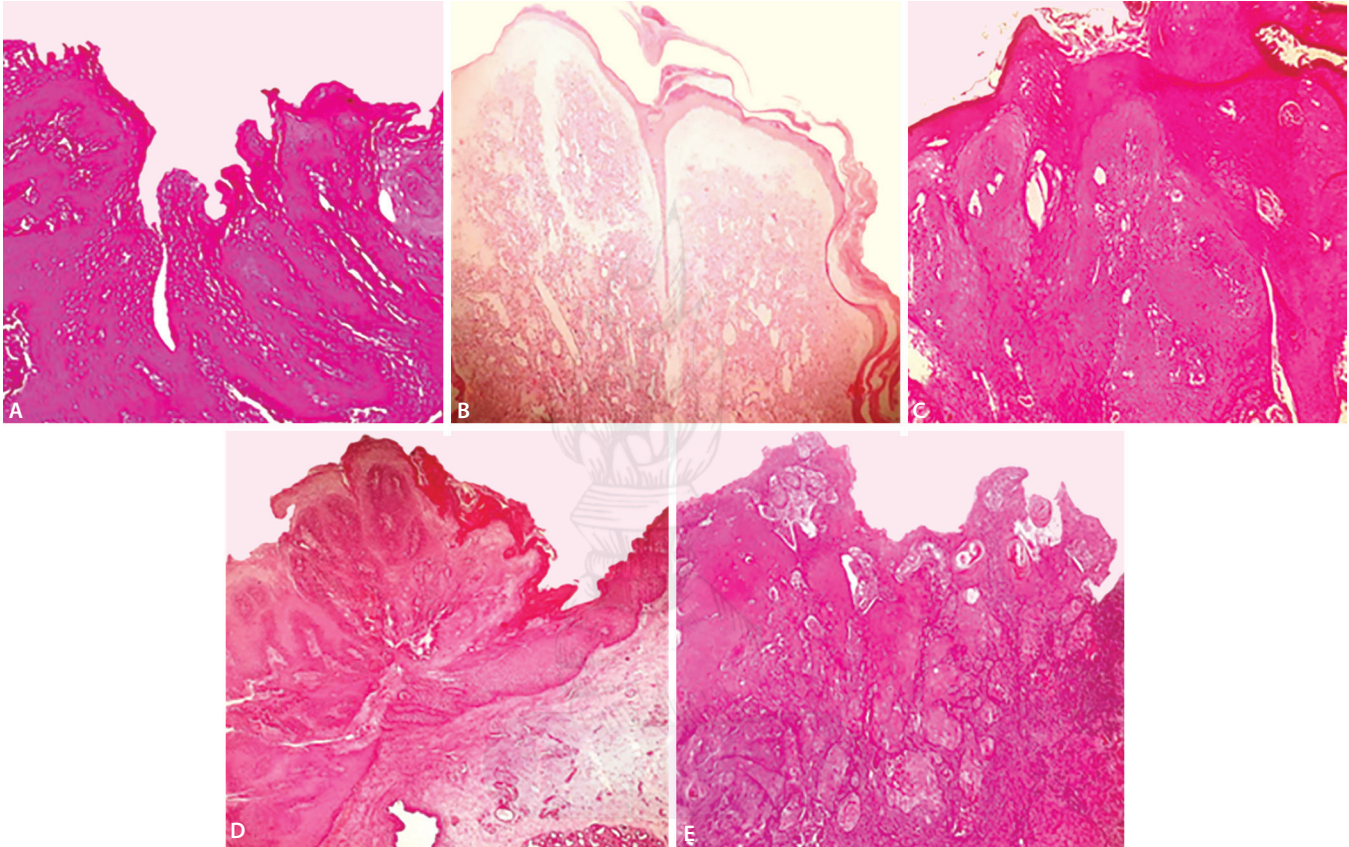
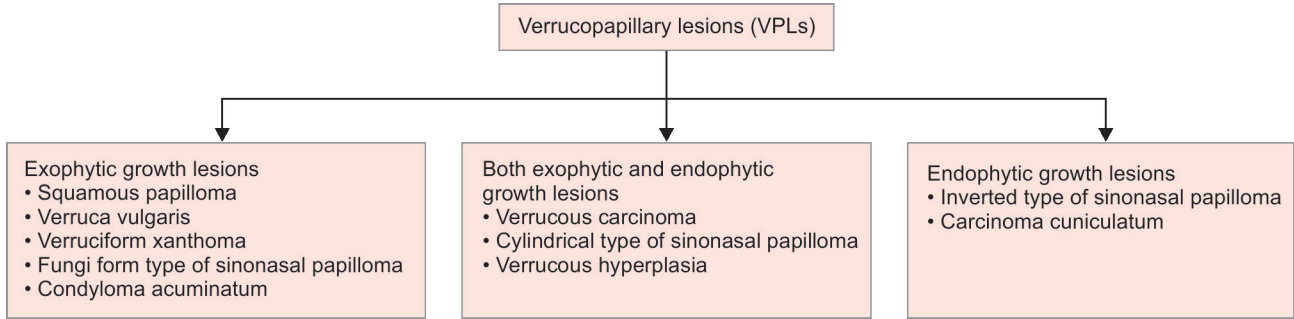
Flow chart 3: Classification of VPLs based on the type of the lesion (Regezi et al, 2003)



Flow chart 4: Classification of VPLs based on the malignant potential (Thomas and Barret, 2009)



Flow chart 5: Classification of VPLs based on growth pattern of oral VPLs (working classification)



Figs 1A to E: Photomicrographs of (A) Squamous papilloma (H & E; X100); (B) Keratoacanthoma (H & E; X100); (C) Verrucous hyperplasia (H & E; X100); (D) Verrucous carcinoma (H & E; X100); (E) Papillary Squamous cell carcinoma (H & E; X100).

rolled margins and distinct collarette. This yields a crateriform or umbilicated appearance. However clinically, these crateriform nodules are not always peculiarized by verrucous or papillary appearance, but histopathological features reveal the acanthotic in folding with keratin crypts. The common focal papillary lesions include squamous papilloma, verruca vulgaris, verruciform xanthoma, keratoacanthoma, warty dyskeratosis, and squamous cell carcinoma.^{1,3-6}

Oral Squamous Papilloma (OSP) (Fig. 1)

Oral squamous papilloma (OSP) is a benign epithelial neoplasm represented as a papillary (or) verruciform mucosal mass which accounts for 3–45% of all biopsied lesions. This exophytic growth is due to the benign proliferation of the stratified squamous epithelium (Table 1).^{1,2}

Verruca Vulgaris

Verruca vulgaris is also represented as “common wart”. It is a persistent lesion of the skin and mucous membrane caused by HPV-2, 4 and 40. It shows benign epidermal proliferation with rare malignant transformation. It is estimated to occur in approximately 7% of the population. It is a contagious disorder and transmitted to the other areas of the body if left untreated (Tables 1 and 2).^{7,8}

Verruciform Xanthoma

Verruciform xanthoma is a benign mucocutaneous lesion showing papillary-like growth pattern frequently involving oral mucosa. The incidence rate is 0.025–0.05%. It usually presents as a verrucous pattern and in some conditions, may show polypoid, sessile or papillomatous appearance (Table 3).

Table 1: Differential diagnosis of oral squamous papilloma

<i>Criteria</i>	<i>Squamous papilloma</i> ^{4,6}	<i>Verruciform xanthoma</i> ⁷	<i>Verruca vulgaris</i> ^{8,9}	<i>Heck's disease</i> ^{4,5}	<i>Pyogenic granuloma</i> ^{4,5}
Common site	Soft palate, tongue, and lip	Alveolar ridge and gingiva	Anterior tongue, vermilion border, and labial mucosa	Labial, buccal and lingual	Gingiva, lower lip and the dorsum of the tongue
Clinical presentation	Cauliflower or wart like appearance	White or red color, papillary or roughed	Painless papule or nodule with papillary projections or plebby surface	Multiple white to pinkish papules	Elevated, pedunculated or sessile vascular mass with smooth, lobulated or warty surface
Histopathology	Finger-like projections resembling keratinized exophytic verrucopapillary processes, acanthosis, and fibrovascular stroma	Stroma exhibits the presence of foamy histiocytes or granular cells	Fingerlike or pointed projections Chronic inflammatory infiltrate in connective tissue cores Produce "cupping effect" Presence of mitosoid cell or bodies	Hyperplastic epithelium with no keratosis Broadening and clubbing of the rete ridges without dysplastic features Presence of mitosoid cell	Thin and atrophic epithelium Proliferating of fibroblasts and budding endothelial cells Fibrinopurulent membrane
Immuno-histochemical markers	p-16, HPV 6 and 11	CD68 and Cathepsin B	HPV -2,4,6,40 P-16, p53, Carcinoembryonic antigen	HPV 13 and 32	ICAM-1, VCAM-1, CD-34 & CD-31

Table 2: Differential diagnosis of verruca vulgaris

<i>Criteria</i>	<i>Verruca vulgaris</i> ^{8,9} and <i>Verruciform xanthoma</i> ^{7,9}	<i>Seborrheic keratosis</i> ^{4,5,9}	<i>Exophytic papillary squamous cell carcinoma</i> ^{2,3,9}	<i>Verrucous carcinoma</i> ^{9,10}
Common site		Although it is a rare lesion, it may occur in buccal mucosa and lip	Oropharynx and nasopharynx	Buccal mucosa, mandibular alveolar crest, gingiva, hard palate, floor of the mouth and tongue
Clinical presentation	Refer Table 1	Thin, translucent and granular or wrinkled appearance	Soft, friable, polypoid, exophytic, papillary tumor	Thick white plaque resembling a cauliflower
Histopathology		Parakeratinized epithelium and absence of hypergranulosis Presence of koilocytes	Papillomatous architecture, cytologic atypia, mitoses and infiltrative growth arrangement keratinizing cord-like and nonkeratinizing ribbon-like patterns Immature Basaloid cells or more pleomorphic cell	Exophytic, soft, fungating growth with a pebbly surface having locally aggressive nature Highly keratinized or parakeratinized with mild epithelial dysplasia Elephant foot rete ridges with pushing margins Exhibits abrupt transition with inward projecting epithelial folds which represents exo and endophytic growth pattern

(Contd...)

(Contd...)

Criteria	<i>Verruca vulgaris</i> ^{8,9} and <i>Verruciform xanthoma</i> ^{7,9}	<i>Seborrheic keratosis</i> ^{4,5,9}	<i>Exophytic papillary squamous cell carcinoma</i> ^{2,3,9}	<i>Verrucous carcinoma</i> ^{9,10}
	Refer Table 1	–	Ki-67, VEGF, MMP-2 and 9, NQO1, CK-8, 13, 18	Cleft like spaces Parakeratin plugging P53, E-cadherin and MMP-1

Table 3: Differential diagnosis of verruciform xanthoma

Criteria	<i>Verruciform xanthoma</i> ^{7,9}	<i>Verrucous carcinoma</i> ^{9,10}	<i>Squamous papilloma and verruca vulgaris</i> ^{4-6,8,9}
Common site	Alveolar ridge and gingiva		
Clinical presentation	White or red color, papillary/verrucous or roughed		
Histopathology	Exhibit verruciform architecture with hyperkeratosis and papillomatous acanthosis Presence of xanthoma cells	Xanthoma cells are absent in Verrucous carcinoma	These entities show different degree of koilocytic change and do not contain lipid-laden macrophages in connective tissue

Table 4: Differential diagnosis of papillary hyperplasia

Criteria	<i>Papillary hyperplasia</i> ¹¹	<i>Nicotinic stomatitis</i> ^{4,5}	<i>Darier's disease</i> ^{4,5}	<i>Cowden's syndrome</i> ^{4,5}
Common site	Palate	Hard palate	larynx and pharynx	Dorsum of the tongue and buccal mucosa
Clinical presentation	Multiple red to pink polyp-like projections	White cobblestone appearance, nonscrapable and have fissuring	Minute, white papules, rough upon palpation	Coalesce into confluent sheets, Smooth, multiple papules
Histopathology	Pseudoepitheliomatous hyperplasia Multiple, small vertical projections with a parakeratotic or orthokeratotic layer Inflammatory infiltrate transmigration into the lower spinous layer	More keratinized Presence of a small red dot or punctum in the center of each nodular excrescence	Dyskeratosis Acanthosis Typical cells–corps ronds and grains	Epithelial hyperplasia No evidence of inflammation
Immunohistochemical markers	–	–	–	PTEN

Multifocal Verrucopapillary Lesions

The common multifocal verrucopapillary lesions include papillary hyperplasia, verrucous carcinoma, papillary exophytic squamous cell carcinoma, focal epithelial hyperplasia, and verruciform leukoplakia.

Papillary Hyperplasia

Papillary hyperplasia is an unusual condition which is also represented as inflammatory papillary hyperplasia, papillomatosis,

pseudoepitheliomatous hyperplasia, denture stomatitis. It is the painless and irreversible lesion most frequently involving the mucosa of the palate and lingual mandibular gingiva. It is always associated with the patients having ill-fitting dentures and poor oral hygiene (Table 4).¹¹

Focal Epithelial Hyperplasia

Focal epithelial hyperplasia (FEH) is a benign contagious disease of the oral mucosa. It normally appears in childhood. It is also



Table 5: Differential diagnosis of focal epithelial hyperplasia

<i>Criteria</i>	<i>Keratoacanthoma</i> ¹² (Fig. 1)	<i>Condyloma Acuminatum</i> ^{1,4,5}	<i>Pseudoepitheliomatous hyperplasia</i> ^{1,4,5}	Verruca vulgaris, squamous papilloma and Verruciform Xanthoma, focal epithelial hyperplasia
Common site	Face	Labial mucosa, soft palate, lingual frenum	Tongue	
Clinical presentation	Solitary, rounded, dome-shaped nodule along with a central keratin plug	Sessile, pink, well-demarcated and exophytic mass	Elevated nodule and raised margins	Refer Table 1
Histopathology	Central crater-like an ulcer Droplet shaped rete ridges Dyskeratosis, basal cell nuclear, hyperchromatism, conspicuous nucleoli, increased mitotic activity with normal morphology, no loss of basal membrane	Acanthotic stratified squamous epithelium Mild keratotic papillary surface projections	Irregular or tongue-like proliferation of the squamous epithelium Jagged margins, or pointed mass exhibiting keratin pearls Invasive acanthosis	
Immunohistochemical markers	CK ¹⁷	-	P53	

Table 6: Differential diagnosis of proliferative verrucous leukoplakia

<i>Criteria</i>	<i>Proliferative Verrucous leukoplakia</i> ^{1,4,5}	<i>Homogeneous leukoplakia</i> ^{4,5}	<i>Others</i>
Common site	Gingiva and palate	Buccal mucosa, palate, and tongue	Other lesions mimicking PVL like frictional keratosis will have a clinically identifiable cause, whereas other entities like squamous papilloma, Verrucous carcinoma, chronic hyperplastic candidiasis, etc., can be diagnosed by their different histological features.
Clinical presentation	White Verrucous slightly raised lesion with a granular texture	Regular, smooth whitish surface and well-defined edges	
Histopathology	Exophytic, a hyperkeratotic lesion with prominent verruciform or papillary surface Acanthosis forming blunt projections into the lamina propria	Epithelial dysplasia	
Immunohistochemical marker	-	EGFR, Cox1&2, P53	

Table 7: Differential diagnosis of verrucous carcinoma and exophytic papillary squamous cell carcinoma

<i>Criteria</i>	<i>Verrucous carcinoma verrucous leukoplakia, squamous papilloma and pseudoepitheliomatous hyperplasia</i>	<i>Verrucous hyperplasia</i> ¹³ (Fig. 6)	<i>Sinonasal papilloma</i> ¹⁵
Common site		Buccal mucosa	Nasopharynx, lacrimal sac, and middle ear space
Clinical presentation	Refer Tables 1,2, 5 and 6	Warty or papillary fungating exophytic mucosal mass	Irregular, friable appearance, unilateral polypoidal mass
Histopathology		Hyperplastic broadened rete ridges lay above the adjacent normal epithelium Two variety: Sharp and blunt No pushing border & parakeratin plugging	Exhibit inflammation with cytologic atypia or even dysplasia with numerous mitotic figures
Immunohistochemical markers		MCM-2 and 5	-

Multifocal Verrucopapillary Lesions

The common multifocal verrucopapillary lesions include papillary hyperplasia, verrucous carcinoma, papillary exophytic squamous cell carcinoma, focal epithelial hyperplasia, verruciform leukoplakia.

Papillary Hyperplasia

Papillary hyperplasia is an unusual condition which is also represented as inflammatory papillary hyperplasia, papillomatosis, pseudoepitheliomatous hyperplasia, denture stomatitis. It is the painless and irreversible lesion most frequently involving the mucosa of the palate and lingual mandibular gingiva. It is always associated with the patients having ill-fitting dentures and poor oral hygiene (Table 4).¹¹

Focal Epithelial Hyperplasia

Focal epithelial hyperplasia (FEH) is a benign contagious disease of the oral mucosa. It normally appears in childhood. It is also termed as Heck's disease or multifocal papilloma. Various studies have reported that the condition remits spontaneously (Table 5).

Proliferative Verrucous Leukoplakia or Verruciform Leukoplakia

Proliferative verrucous leukoplakia (PVL) is an uncommon form of oral leukoplakia. It was first stated in 1985 by Hansen which develops initially as a white plaque of hyperkeratosis that eventually becomes a multifocal disease with confluent, exophytic and proliferative features. PVL shows specific characteristics, mainly a more aggressive biological behavior than other forms of leukoplakia. It is expressed by a tendency toward multifocality, a high probability of recurrence and a high rate of malignant transformation. It is defined as a continuum of oral epithelial disease with hyperkeratosis at one end of a clinical and microscopic spectrum and verrucous carcinoma or squamous cell carcinoma at the other (Table 6).^{4,5}

Verrucous Carcinoma and Exophytic Papillary Squamous Cell Carcinoma (Fig. 1)

Oral verrucous carcinoma is a special form of well-differentiated squamous cell carcinoma. It was first described in 1948 by Lauren V Ackermann. Different names are used in the literature to describe this entity, including Ackerman's tumor, Buschke-Loewenstein tumor, florid oral papillomatosis, epithelioma cuniculatum, and carcinoma cuniculatum. It exhibits both exophytic and endophytic growth patterns (Table 7).³⁻⁵

The most common malignancy of the upper aerodigestive tract is squamous cell carcinoma (SCC). Crissman et al. proposed the term papillary carcinoma, and it is the rare variant of SCC. Currently, the WHO classification named this lesion as papillary SCC (PSCC). This is described in other parts of the body including skin, uterine, cervix, conjunctiva of the eye and thymus. In the upper aerodigestive tract, it occurs most commonly in the larynx. It is an apparent variant characterized by exophytic and papillary growth with a favorable prognosis.^{3,4,5,14}

CONCLUSION

Verrucopapillary lesions of the oral cavity present a diagnostic dilemma because of similar clinical presentation. To achieve an accurate diagnosis, oral pathologists should have a sound knowledge about histopathology and biological behavior of these. This article features the unique characteristics of oral verrucopapillary lesions with respect to its intraoral location, clinical presentation, histopathology and specific Immunohistochemical markers that provide an aid for definitive diagnosis and treatment.

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