

## REVIEW

# Exophytic Verrucous Hyperplasia of the Oral Cavity – Application of Standardized Criteria for Diagnosis from a Consensus Report

Rosnah Binti Zain<sup>1\*</sup>, Thomas George Kallarakkal<sup>1</sup>, Anand Ramanathan<sup>1</sup>, Jin Kim<sup>2</sup>, WM Tilakaratne<sup>3</sup>, Takashi Takata<sup>4</sup>, Saman Warnakulasuriya<sup>5</sup>, Vinay Kumar Hazarey<sup>6</sup>, Alison Rich<sup>7</sup>, Haizal Mohd Hussaini<sup>7</sup>, Ajura Jalil<sup>8</sup>

## Abstract

Verruco-papillary lesions (VPLs) of the oral cavity described in the literature involve a spectrum of conditions including squamous papilloma, verruca vulgaris, focal epithelial hyperplasia, condyloma, proliferative verrucous leukoplakia and verrucous carcinoma. A majority of the VPLs are slow growing, benign in nature and have a viral aetiology. Virus associated benign mucosal outgrowths are not too difficult to diagnose either clinically or by microscopy. Apart from virus-associated lesions, VPLs harboring malignant potential or behaviour such as verrucous carcinoma, proliferative verrucous leukoplakia, oral verrucous hyperplasia (OVH), oral papillary squamous cell carcinoma (PSCC) and oral conventional squamous cell carcinoma with papillary features (CSCC) need to be further clarified for better understanding of their predictable biologic behavior and appropriate treatment. Current understanding of potentially malignant VPLs is perplexing and is primarily attributed to the use of confusing and unsatisfactory terminology. In particular, the condition referred to as oral verrucous hyperplasia (OVH) poses a major diagnostic challenge. OVH represents a histopathological entity whose clinical features are not well recognised and is usually clinically indistinguishable from a verrucous carcinoma and a PSCC or a CSCC. A consensus report published by an expert working group from South Asia as an outcome of the 'First Asian Regional Meeting on the Terminology and Criteria for Verruco-papillary Lesions of the Oral Cavity' held in Kuala Lumpur, Malaysia, recognised the clinical description of these OVH as a new entity named 'Exophytic Verrucous Hyperplasia'. Previously described clinical features of OVH such as the 'blunt' or 'sharp' variants; and the 'mass' or 'plaque' variants can now collectively fall under this newly described entity. This paper discusses in detail the application of the standardized criteria guidelines of 'Exophytic Verrucous Hyperplasia' as published by the expert group which will enable clinicians and pathologists to uniformly interpret their pool of OVH cases and facilitate a better understanding of OVH malignant potential.

**Keywords:** Verrucopapillary lesions - verrucous hyperplasia - proliferative verrucous leukoplakia - malignant potential

*Asian Pac J Cancer Prev*, 17 (9), 4491-4501

## Introduction

Verrucopapillary lesions (VPLs) of the oral cavity include benign, potentially malignant and frankly malignant disorders. Clinical and histopathological diagnosis of these lesions is challenging. At presentation they may mimic an invasive cancer while histopathological features of a conventional oral squamous cell carcinoma may be absent (Kallarakkal et al., 2013). VPLs of the

oral mucosa usually appear as whitish or pinkish elevated oral mucosal masses having a papillary or a verrucous surface (Hwang et al., 2012). Oral VPLs with a viral etiology include the more common squamous papillomas, verruca vulgaris, and condylomas. Histologically benign oral VPLs usually measure less than 10mm in maximum dimension and present little diagnostic difficulty (Thomas and Barrett, 2009; Hwang et al., 2012). Larger oral VPLs with HPV infection that are equal to or larger than 10mm

<sup>1</sup>Oral Cancer Research and Coordinating Centre & Department of Oro-Maxillofacial Surgical and Medical Sciences, Faculty of Dentistry, University of Malaya, <sup>8</sup>Stomatology Unit, Institute for Medical Research, Kuala Lumpur, Malaysia, <sup>2</sup>Department of Oral Pathology, Oral Cancer Research Institute, Yonsei University College of Dentistry, Seoul, Korea, <sup>3</sup>Centre for Research in Oral Cancer, Faculty of Dental Sciences, University of Peradeniya, Sri Lanka, <sup>4</sup>Department of Oral and Maxillofacial Pathobiology, Institute of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan, <sup>5</sup>Department of Oral Medicine, King's College London, WHO Collaborating Centre for Oral Cancer, London, United Kingdom, <sup>6</sup>Department of Oral Pathology and Microbiology, Government Dental College and Hospital, Nagpur, India, <sup>7</sup>Department of Oral Diagnostic and Surgical Sciences, Dental School Health Sciences, University of Otago, New Zealand \*For correspondence: rosnaibz12@gmail.com

exhibit a risk for malignant transformation (Hwang et al., 2012). Potentially malignant oral VPLs include verrucous hyperplasia (VH), proliferative verrucous leukoplakia (PVL) whereas malignant lesions include verrucous carcinoma, papillary squamous cell carcinoma and carcinoma cuniculatum (Thomas and Barrett, 2009).

Oral verrucous hyperplasia (OVH) is plagued by a lack of unanimity in terminology and poor recognition of its clinical and histopathological features. This clearly reflects the lack of a well-defined set of diagnostic criteria and standardized interpretation of the criteria for OVH. Diagnostic challenges arise in differentiating between OVH, Oral Verrucous Carcinoma (OVC), Papillary Squamous Cell carcinoma (PSCC) and Conventional Squamous Cell Carcinoma with Papillary features (CSCC), especially in situations of poorly oriented samples, insufficient tissues submitted and biopsies lacking normal margins. OVH is less frequently encountered in Pathology services in Europe or North America, but is increasingly represented from the South East Asian Region.

## Differential Diagnosis

A number of oral VPLs have been recognised and described in the literature since the first description of OVC by Ackerman in 1948. These oral VPLs may have similar clinical profiles, however, may exhibit variations in size, colour and surface texture at the different locations. Discriminatory histopathological diagnosis of these lesions would require the presence of normal margins and is still considered as the 'gold standard' while immunohistochemical panels have been considered as adjuncts for diagnosis of difficult cases. Discriminating these lesions histologically by incisional biopsy remains a challenge especially in poorly orientated specimens and where the adjacent normal margins were not included (Klieb and Raphael, 2007).

Oral squamous papillomas may affect any intraoral site and are usually less than 10 mm in size. They usually have a narrow base and a broad papillary surface. They tend to lack much keratinization, contain prominent fibrovascular cores and exhibit minimal cytological atypia (Thompson et al., 1999; Thomas and Barrett, 2009). Koilocytes are noted infrequently. HPV types 6 & 11 are the putative etiologic agents (Chen et al., 2006).

Oral verrucous hyperplasia (OVH) was originally described by Shear and Pindborg in 1980 (Yeh, 2003). A study on Taiwanese patients reported a strong association between OVH with areca quid and smoking habits. The buccal mucosa was the most commonly affected site. A malignant transformation rate of 3.1% and mean malignant transformation duration of 54.6 months was reported in their series of cases (Wang et al., 2009). For this reason OVH is considered a potentially malignant disorder. OVH presents as a whitish or pink elevated oral mucosal plaque or mass with a verrucous or papillary surface and has been traditionally classified into two variants namely the sharp and the blunt variety. The sharp variety comprising of long, narrow, and heavily keratinized verrucous processes appears white as a result of heavy keratinization while

the blunt variety consists of verrucous processes that are broader, flatter, and not heavily keratinized. Leukoplakia was an integral component of the lesion and elsewhere in the mouth of the patients who manifested any or both of these variants (Shear and Pindborg, 1980). Wang et al., (2009) reclassified OVH into a plaque type and mass type primarily based on their histopathological features. The histopathological criteria favouring a diagnosis of OVH included epithelial hyperplasia with parakeratosis or hyperkeratosis and a verrucous surface, and (ii) absence of down growth of hyperplastic epithelium into the lamina propria as compared with adjacent normal mucosal epithelium (Wang et al., 2009). A surface keratin layer of >40 microns was used to differentiate the mass and the plaque types. Epithelial dysplasia was uniformly present in both the variants of OVH. It was reported that the mass type of OVH described by Wang et al., (2009) exhibited a greater tendency for malignant transformation. Shear and Pindborg, (1980) observed a risk of malignant transformation in their series even though no specific difference was observed between the two variants. Based on the available literature, it is apparent that the terminologies used to describe these lesions are confusing. This was also reflected in the report by Wang et al., (2009) who termed the plaque-type OVH as oral verruciform leukoplakia and preferred to reserve the diagnosis of OVH only for the mass type lesions.

Proliferative verrucous leukoplakia (PVL), an aggressive form of oral leukoplakia that has a protracted growth phase, was first described by Hansen et al in 1985 (Hansen et al., 1985). PVL and OVH are interrelated lesions and both have been shown to progress to malignancy (Batsakis et al., 1999). However, both these terminologies are neither clinically and histopathologically interchangeable since PVL does not have a single defining histopathology and is more a clinically preferred term whereas, OVH has to be diagnosed histopathologically (Shear and Pindborg, 1980; Klanrit et al., 2007). Histopathologically the evolutionary spectrum of PVL may range from epithelial hyperkeratosis/hyperplasia to dysplasia to frank carcinoma (verrucous or PSCC/CSCC) (Hansen et al., 1985; Jacobson et al., 1996). OVH may be a histologic component within this evolutionary spectrum of PVL (Jacobson et al., 1996; Klanrit et al., 2007). A definitive diagnosis of PVL is always retrospective due to the lack of clinical and histological diagnostic criteria (Batsakis et al., 1999; Klanrit et al., 2007). Fridell and Rosenthal in 1941 used the term verrucoid to designate an oral VPL where a well-differentiated squamous cell carcinoma of the oral cavity was termed as "papillary verrucoid carcinoma". Ackerman in 1948 is credited with the description and coining of the terminology 'verrucous carcinoma' (OVC) which is a low-grade variant of squamous cell carcinoma. OVC differs from OVH in having an exophytic and an endophytic growth pattern whereas OVH exhibits exophytic growth only. OVC further differs from OVH in the morphology of rete processes, which are broad, elongated, resembling elephant's feet while in OVH the rete processes are pointed, ragged, slender and anastomosing (Thomas and Barrett, 2009). Many reports have recognized that marked

cytological atypia/ dysplasia are not features of OVC but minimal dysplastic features could still be present. OVH however may or may not manifest epithelial dysplasia (Shear and Pindborg, 1980; Slootweg and Müller, 1983). In the series reported by Shear and Pindborg (1980) it was observed that 66% of OVHs had dysplasia. It may be noted that if some of the OVHs did transform into OVC, then it would be difficult to explain as to how these dysplastic OVHs transform into OVCs which have minimal cellular atypia. The possibility that the majority of OVCs do not manifest focus/foci of cellular atypia or mild dysplasia may be the result of a non-representative biopsy or incomplete sampling of the surgical OVC specimens. The presence of foci of cellular atypia (which may have been missed in an incisional biopsy) in OVC could better explain this phenomenon of transformation of OVH (with atypia and mild dysplastic features) to OVC.

At times the term OVH may be used as a 'holding' diagnosis when a diagnosis of OVC, PSCC/CSCC are considered but could not be confirmed due to an inadequate biopsy specimen without the pushing deep margins or frank invasion respectively not being apparent. In such cases the pathology report should reflect that an OVC or PSCC/CSCC is not ruled out and a further biopsy may be required for a definitive diagnosis (Schrader and Laberke, 1988). Lesions with dominant features of verrucous carcinoma that present foci/focus of conventional invasive squamous cell carcinoma has led authors to consider them as a 'hybrid' form of OVC or SCC with verrucoid features (Koch et al., 2001). However, with the presence of foci of conventional SCC in OVC, these lesions should be diagnosed as conventional OSCC (CSCC) to facilitate more radical treatment protocols that are in practice for the management of a conventional OSCC. Therefore it is strongly recommended to thoroughly sample the surgical specimen of an OVC so as not to miss the foci of SCC (Kallarakkal et al., 2013).

Papillary SCC is an invasive SCC (PSCC), with an exophytic papillary component (Ferlito et al., 1999) and absence of keratinization: the latter being the hallmark of this lesion (Suarez et al., 2000; Jo et al., 2009). PSCC has a high recurrence rate and an increased incidence for secondary tumours. Despite its increased tendency for loco-regional recurrence, papillary squamous cell carcinomas have an excellent prognosis. It may be observed that the recurrent lesions do not demonstrate the same histopathology as the primary PSCC and may have features of conventional SCC (Jo et al., 2009; Russell et al., 2011). It has been suggested that PSCC could be a harbinger of a widespread mucosal defect that can manifest features of conventional SCC (with papillary features - CSCC) or PSCC (Russell et al., 2011).

Carcinoma Cuniculatum (CC) is a rare variant of carcinoma, which was first described in 1954 (Burkhardt, 1986). It is regarded as a subtype of SCC (Burkhardt, 1986) or a variant of OVC (Allon et al., 2002). It is described as an inverted OVC having similar bland cytological features, good differentiation and very little atypia like OVC. It differs from PSCC, which has cytological features of malignancy, atypical and increased mitosis. CC and OVC differ from PSCC in the degree

of keratinization with CC and OVC having prominent keratinization. However, CC and OVC differ from each other in the pattern of keratinization with OVC having vertical keratinization described as "church-spire-like" and CC having complex branching keratin-filled crypts. These crypts tend to discharge yellow foul-smelling secretions. Microabscesses in large keratin masses are also seen in CC (Brown and Freeman, 1976; Ferlito et al., 1999; Allon et al., 2002).

In order to verify the potential for malignant change of OVH, there is a need to standardise across the region its clinical and histopathological diagnostic criteria. This will enable the clinicians and pathologists to diagnose and follow-up the pool of these cases by applying a set of well-defined criteria. There have been recent reports of OVH presenting minimal evidence of dysplasia (Woo et al., 2014). Proper follow-up data of these patients would allow critical analysis of the potential malignant behaviour of OVH, thus facilitating its inclusion into the OPMD group in future WHO classification. Thus, the first Asian Consensus meeting on Terminology and Diagnostic Criteria of Verrucous Papillary Lesions of the Oral Cavity was organized aiming to address this issue by going back to basics of clinical diagnosis and histopathological interpretation for recognizing OVH.



**Figure 1. Macroscopic Appearance.** A): Exophytic Verrucous Hyperplasia showing exophytic fleshy verrucopapillary outgrowth with a white and/or pink surface color. B): Exophytic Verrucous Hyperplasia showing mixed features of fleshy exophytic verrucopapillary outgrowth with a white and/or pink surface color and a white, plaque-like exophytic verrucous lesion

**Table 1. Guide to Histological Diagnosis of VPL**

Histological Diagnosis	OVC	PSCC	CSCC	OVH	SCP
Clinical size of lesion	> 1 cm	> 1 cm	> 1 cm	≥1 cm	< 1 cm
Histological Criteria:					
Keratinized exophytic verruco-papillary processes	Y	Y*	Y	Y	Y
Epithelium is hyperplastic (basal cell hyperplasia and acanthosis)	Y	Y	Y	Y	Y
Growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium	Y	Y	Y	N	N
Epithelial Dysplasia/cellular atypia	N**	Y	Y	Y/N	N
Subepithelial lymphocytic infiltration	Y	Y/N	Y/N	Y/N	Y/N
Frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium showing pushing border effect)	Y	N	N	N	N
Prominent fibrovascular core	N	Y	N	N	Y
Invasion	N	Y	Y	N	N
Keratin plugging	Y	N	Y	Y/N	N

(ii) A diagnosis of oral verrucous hyperplasia (OVH) should be made only when there is an absence of growth of the hyperplastic epithelium into the lamina propria as compared with the level of the basement membrane of the adjacent normal epithelium; (iii) Oral verrucous hyperplasia (OVH) should be clearly differentiated from oral verrucous carcinoma (OVC) where OVC exhibits frank downward growth of the epithelial processes below the level of the basement membrane of the adjacent normal epithelium. OVC can be differentiated from Papillary squamous cell carcinoma (PSCC)/CSCC by the presence of invasion and cytologic atypia; (iv) Oral verrucous hyperplasia(OVH) should be differentiated from squamous cell papilloma (SCP) by its size and by the presence of a prominent fibrovascular core in the latter; (v) \* Verrucous exophytic processes with minimal or absence of keratinization; (vi) \*\*Mild cellular atypia has been reported in cases of OVC.

The three-day workshop culminated in the development of a comprehensive clinicopathological guideline for the diagnosis of OVH that could be tested in regional participating centers. A preliminary report was issued on Consensus on Terminology and Criteria (Zain R.B., 2013).

#### *Clinical criteria for verrucous hyperplasia of the oral cavity*

The clinical profile of OVH may be similar to other verrucopapillary lesions exhibiting variations in size, colour and surface texture with locations being in similar areas as the OVC i.e. mostly in the buccal mucosa followed by the tongue, palate, gingiva and labial mucosa (Wang et al., 2009). The OVH appearing as a whitish plaque with verrucous surface have been clinically recognized as Verrucous Leukoplakia. However, it may not be appropriate to denote OVH appearing as exophytic lesions with pinkish color, as Verrucous Leukoplakia. In addition, the use of the term Verrucous Hyperplasia as a clinical term is thought to be confusing as it actually described the histopathological profile of this lesion. Thus, the working committee proposed the term “Exophytic Verrucous Hyperplasia” to denote the clinical entity that represents the microscopic diagnosis of OVH. The following criteria for the clinical diagnosis of OVH were proposed:

a) These lesions clinically present in two forms: i) as an exophytic, fleshy verruco-papillary outgrowth with a white and/or pink surface color (Figure 1a) and ii) as a white, plaque-like exophytic verrucous lesion (Figure 1b). The latter may mimic verrucous leukoplakia. In both instances the clinical term ‘exophytic verrucous hyperplasia’ should be used.

b) Exophytic verrucous hyperplasia may occur in any anatomical site in the oral cavity and in general would be more than 1 cm in size.

c) Unlike proliferative verrucous leukoplakia (PVL) exophytic verrucous hyperplasia is a discrete and solitary lesion.

d) Exophytic verrucous hyperplasia may co-exist in a patient presenting with oral submucous fibrosis.

e) The clinical presentation of exophytic verrucous hyperplasia could masquerade as a squamous cell carcinoma or verrucous carcinoma. Absence of induration is a cardinal feature of exophytic verrucous hyperplasia.

#### *Histological criteria for verrucous hyperplasia of the oral cavity*

The working committee proposed the following criteria for the histological diagnosis of oral verrucous hyperplasia:

a) Keratinized exophytic verruco-papillary processes seen. Keratin plugging may be present.

b) Epithelium is hyperplastic with both basal cell hyperplasia and acanthosis.

c) Absence of downward growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium.

d) Epithelial dysplasia may or may not be present.

e) Subepithelial lymphocytic infiltration as a host response may or may not be present.

f) Verrucous hyperplasia should be clearly differentiated from verrucous carcinoma which exhibits frank downward growth of the epithelial processes below the level of the basement membrane of the adjacent normal epithelium.

g) Verrucous hyperplasia should be differentiated from squamous cell papilloma by its size and by the presence of a prominent fibrovascular core in the latter.

h) In a small biopsy without adjacent normal mucosal epithelium particular attention should be paid to exclude



Figure 2. a): Example 1 - Photomicrograph of Squamous Cell Papilloma

Table 2 (a): Description/Histological Criteria for Example 1 - Squamous Cell Papilloma

Description/Histological Criteria		
a	Keratinized exophytic verruco-papillary processes	Y
b	Epithelium is hyperplastic (basal cell hyperplasia and acanthosis)	Y
c	Growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium	N
d	Epithelial Dysplasia /cellular atypia	N
e	Subepithelial lymphocytic infiltration	N
f	Frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium showing pushing border effect	N
g	Prominent fibrovascular core	Y
h	Invasion	N
i	Keratin plugging	N
Y-Yes; N- No; UA – Unable to assess		

Diagnosis at excisional biopsy: Squamous cell papilloma: Yes (presence of criteria a, b, g and clinical size<1cm)

other pathologies such as squamous cell papilloma and verrucous carcinoma.

It was proposed by the working committee that of the above, criteria (a), (b) and (c) must be present to make a histopathological diagnosis of OVH. Further it was recommended that the pathology report should include a statement describing the degree of dysplasia if present and a cautionary note to say that OVH may recur following excision and may progress to verrucous carcinoma and squamous cell carcinoma. Therefore careful surveillance is mandatory.

Arising from this Consensus report, it is suggested

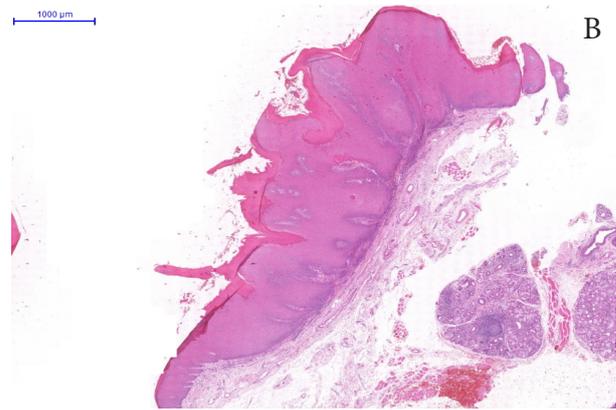


Figure 2. b): Example 2 - Photomicrograph of Oral Verrucous Hyperplasia at incisional biopsy

Table 2 (b): Description/Histological Criteria for Example 2 - Oral Verrucous Hyperplasia at incisional biopsy

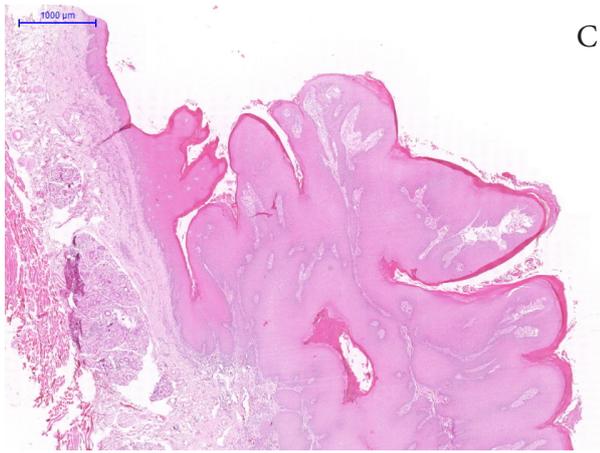
Description/Histological Criteria		
a	Keratinized exophytic verruco-papillary processes	Y
b	Epithelium is hyperplastic (basal cell hyperplasia and acanthosis)	Y
c	Growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium	N
d	Epithelial Dysplasia /cellular atypia	N
e	Subepithelial lymphocytic infiltration	N
f	Frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium showing pushing border effect	N
g	Prominent fibrovascular core	N
h	Invasion	N
i	Keratin plugging	Y
Y-Yes; N- No; UA – Unable to assess		

Diagnosis at incisional biopsy: Verrucous hyperplasia (presence of criteria a,b and absence of c & f); Other diagnosis excluded; 1) Squamous cell papilloma: Absence of criteria g and clinical size of >1cm, 2) Verrucous Carcinoma: Absence of f, 3) Papillary Squamous cell carcinoma/Conventional Squamous cell carcinoma with papillary features: Absence of h

that the interpretation of the VPL is as presented in Table 1 below:

## Discussion

The recognition of exophytic oral verrucous hyperplasia among betel quid (areca nut) chewers amounts to the identification of a new disease entity, one with rapid increase in incidence and one that poses important research questions. The challenges posed include clinical and pathology diagnosis and accurately differentiating OVH from other verrucopapillary oral lesions and to manage these in the light of potential malignancy. To that end the expert group discussed the differential diagnosis, the application of suggested criteria and some case



**Figure 2. c): Example 2 - Photomicrograph of Oral Verrucous Hyperplasia at excisional biopsy**

**Table 2 (c): Description/Histological Criteria for Example 2 – Oral Verrucous Hyperplasia at excisional biopsy.**

Description/Histological Criteria		
a	Keratinized exophytic verruco-papillary processes	Y
b	Epithelium is hyperplastic (basal cell hyperplasia and acanthosis)	Y
c	Growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium	N
d	Epithelial Dysplasia /cellular atypia	N
e	Subepithelial lymphocytic infiltration	N
f	Frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium showing pushing border effect	N
g	Prominent fibrovascular core	N
h	Invasion	N
i	Keratin plugging	N
Y-Yes; N- No; UA – Unable to assess		

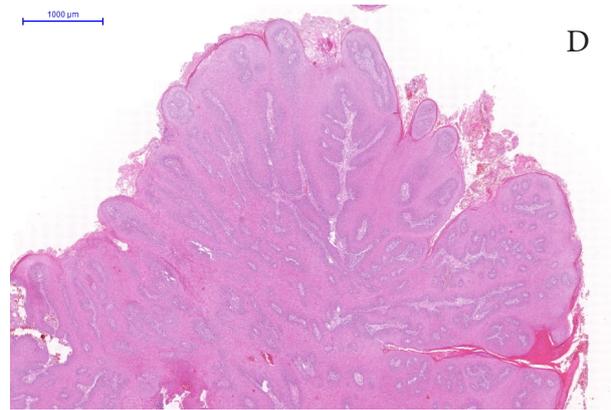
Diagnosis at excisional biopsy: Verrucous hyperplasia (presence of criteria a,b and absence of c)

presentations to illustrate pathognomic features of OVH and how they differ from other verucopapillary lesions. The following examples are presented to illustrate the application of the main diagnostic criteria suggested by the expert panel based on the matrix shown in Table 1 above.

*Application of suggested Criteria (Kuala Lumpur Consensus) (Zain R.B., 2013)*

The following examples are presented to illustrate the application of the suggested criteria based on the tabulated matrix shown in Table 1 above.

Example 1: This is a case of clinically recognised squamous cell papilloma with a cauliflower-like surface appearance of clinical size of 0.6 cm. Histologically only two differential diagnoses i.e. SCP and OVH could be considered for this case as there is presence of keratinized



**Figure 2. d): Example 3 - Photomicrograph suggestive of Oral Verrucous Hyperplasia at incisional biopsy**

**Table 2 (d): Description/Histological Criteria for Example 3 - suggestive of Oral Verrucous Hyperplasia at incisional biopsy.**

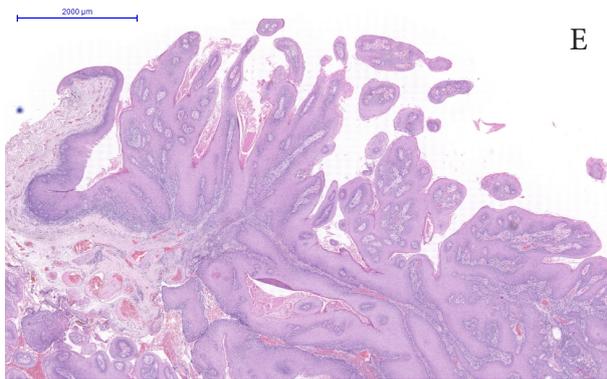
Description/Histological Criteria		
a	Keratinized exophytic verruco-papillary processes	Y
b	Epithelium is hyperplastic (basal cell hyperplasia and acanthosis)	Y
c	Growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium	UA
d	Epithelial Dysplasia /cellular atypia	N
e	Subepithelial lymphocytic infiltration	N
f	Frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium showing pushing border effect	UA
g	Prominent fibrovascular core	N
h	Invasion	UA
i	Keratin plugging	Y
Y-Yes; N- No; UA – Unable to assess		

Diagnosis at incisional biopsy: Verrucous hyperplasia (presence of criteria a,b and absence of c). Other diagnosis excluded;

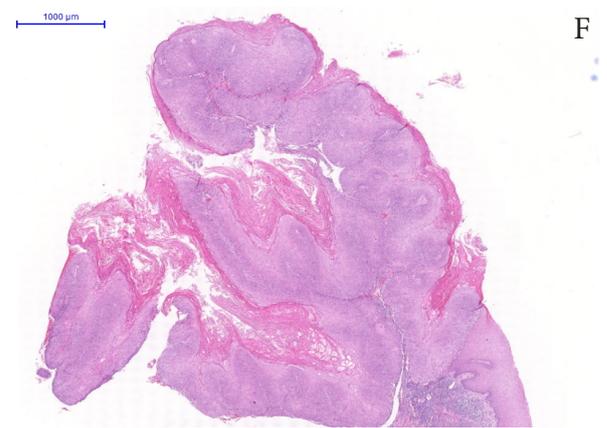
1) Squamous cell papilloma: Absence of criteria g and clinical size of >1cm; 2) Verrucous Carcinoma: Absence of f; 1) Papillary Squamous cell carcinoma/ Conventional Squamous cell carcinoma with papillary features: Absence of h. UA as there is no normal adjacent epithelium present

exophytic verruco-papillary processes with hyperplastic epithelium supported by vascular connective tissue core in the absence of growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium. However, final diagnosis of SCP is the favoured diagnosis because of prominent fibrovascular cores and a clinical size of less than 1 cm. Figure 2 (a) & Table 2 (a) illustrates the use of these criteria in differentiating squamous cell papilloma from verrucous hyperplasia.

Example 2: In example 2 the incisional biopsy shows the presence of keratinized exophytic verruco-papillary



**Figure 2. e): Example 3 - Photomicrograph of definitive diagnosis of Oral Verrucous Hyperplasia at excisional biopsy**



**Figure 2. f): Example 4 - Photomicrograph of Conventional Squamous Cell Carcinoma with papillary features at incisional biopsy**

**Table 2 (e): Description/Histological Criteria for Example 3 - definitive diagnosis of Oral Verrucous Hyperplasia at excisional biopsy**

Description/Histological Criteria		
a	Keratinized exophytic verruco-papillary processes	Y
b	Epithelium is hyperplastic (basal cell hyperplasia and acanthosis)	Y
c	Growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium	N
d	Epithelial Dysplasia /cellular atypia	Y
e	Subepithelial lymphocytic infiltration	Y
f	Frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium showing pushing border effect	N
g	Prominent fibrovascular core	Y
h	Invasion	N
i	Keratin plugging	Y
Y-Yes; N- No; UA – Unable to assess		

a)Diagnosis at excisional biopsy: Verrucous hyperplasia (presence of criteria a,b and absence of c). Diagnosis re-considered and excluded: Squamous cell papilloma (although there is presence of prominent vascular cores, this diagnosis was excluded since the clinical size is > 1cm)

processes with hyperplastic epithelium. At one of the margins there is absence of growth of the hyperplastic epithelium into the lamina propria; whilst the other margin showed a slight hyperplastic epithelial growth into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium. However, there is no frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium (producing pushing border effect) indicative of OVC. In addition there is no frank invasion indicative of PSCC/CSCC, therefore this was diagnosed as Verrucous Hyperplasia in view of the presence of exophytic processes, hyperplastic epithelium and the absence of hyperplastic epithelial growth into the lamina propria as illustrated in Figure 2 (b) and Table 2 (b).

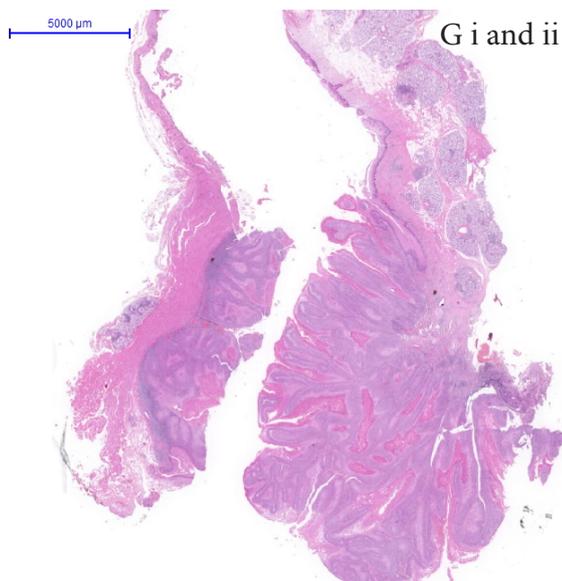
**Table 2 (f): Description/Histological Criteria for Example 4 - Conventional Squamous Cell Carcinoma with papillary features at incisional biopsy**

Description/Histological Criteria		
a	Keratinized exophytic verruco-papillary processes	Y
b	Epithelium is hyperplastic (basal cell hyperplasia and acanthosis)	Y
c	Growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium	Y
d	Epithelial Dysplasia/cellular atypia	Y
e	Subepithelial lymphocytic infiltration	Y
f	Frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium showing pushing border effect	N
g	Prominent fibrovascular core	N
h	Invasion	Y
i	Keratin plugging	Y
Y-Yes; N- No; UA – Unable to assess		

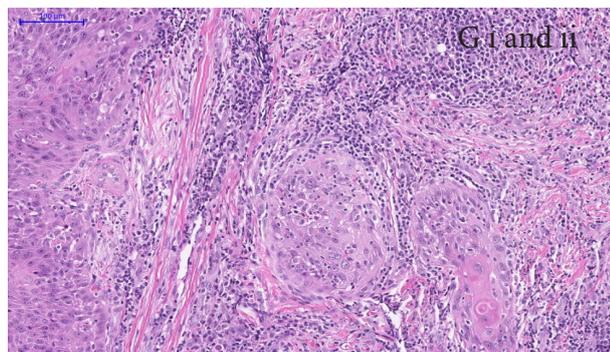
Diagnosis at incisional biopsy: Conventional squamous cell carcinoma with papillary features (presence of a [with marked keratinization], c, d, h and i). Other diagnosis excluded; 1) Papillary Squamous Cell Carcinoma Presence of histological criteria a (although a is present, there is minimal keratinization), and absence of histological criteria g; 2) Verrucous Carcinoma: Absence of histological criteria f; 3) Squamous cell papilloma: Presence of histological criteria i; 4) Verrucous hyperplasia: Presence of histological criteria i

The excision of the lesion confirmed the diagnosis of verrucous hyperplasia since the surgical case satisfied all the criteria for the diagnosis of verrucous hyperplasia as illustrated in Figure 2 (c) and Table 2 (c).

Example 3: The incisional biopsy for this case shows the presence of keratinized exophytic verruco-papillary processes with hyperplastic epithelium. There is no adjacent normal margin evident, thus the inability to access the hyperplastic epithelial growth and the frank downward growth (to rule out verrucous carcinoma) in this case. Whilst the absence of margins also led to the



**Figure 2. G i and ii): Example 4 - Photomicrograph of Conventional Squamous Cell Carcinoma with papillary features at excisional biopsy**



**Figure 2. G i and ii): Example 4 - Photomicrograph of Conventional Squamous Cell Carcinoma with papillary features at excisional biopsy**

inability of assessing for frank invasion, there is however, no cytological atypia observed. Thus, as mentioned earlier, an interpretation suggestive of verrucous hyperplasia is favoured and used as a ‘holding diagnosis’ (Figure 2 (d) and Table 2 (d)), as it was not possible to assess whether there is frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium (producing pushing border effect) indicative of Verrucous carcinoma, and also not possible to assess for frank invasion indicative of PSCC/CSCC. A squamous cell papilloma may be considered in this situation but was excluded due to absence of prominent fibrovascular core and the clinical size being more than 1 cm.

The excisional biopsy of the case showed adjacent normal margins with histological characteristics supporting the diagnosis of verrucous hyperplasia as illustrated in Figure 2 (e) and Table 2 (e).

Example 4: In this example the incisional biopsy shows the presence of keratinized exophytic verruco-papillary processes with hyperplastic epithelium, frank invasion and cytological atypia. A diagnosis of conventional

**Table 2 (g): Description/Histological Criteria for Example 4 - Conventional Squamous Cell Carcinoma with papillary features at excisional biopsy.**

Description/Histological Criteria		
a	Keratinized exophytic verruco-papillary processes	Y
b	Epithelium is hyperplastic (basal cell hyperplasia and acanthosis)	Y
c	Growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium	Y
d	Epithelial Dysplasia/cellular atypia	Y
e	Subepithelial lymphocytic infiltration	Y
f	Frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium showing pushing border effect	N
g	Prominent fibrovascular core	N
h	Invasion	Y
i	Keratin plugging	Y

Y-Yes; N- No; UA – Unable to assess

Diagnosis at excisional biopsy: Conventional squamous cell carcinoma with papillary features (presence of criteria c, d, h and i)

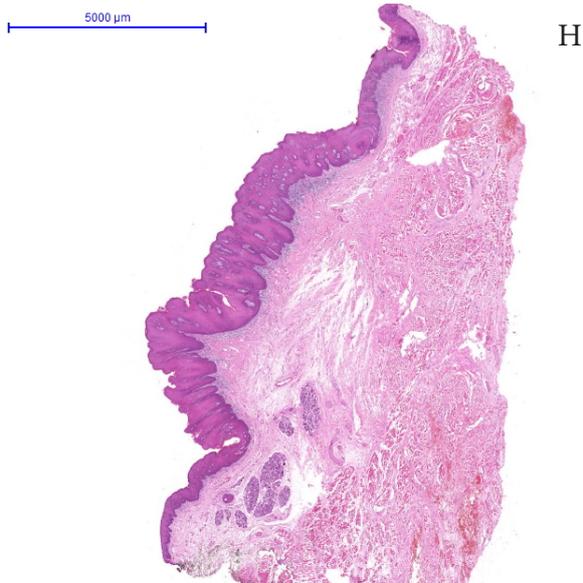
squamous cell carcinoma was confirmed as illustrated in Figure 2 (f) and Table 2 (f). With the presence of frank invasion, the diagnosis of squamous cell papilloma, verrucous carcinoma and verrucous hyperplasia were ruled out. Marked surface keratinization in the present case deferred a diagnosis of PSCC and a diagnosis of CSCC was preferred.

The excisional biopsy demonstrated the presence of frank invasion and cytologic atypia as illustrated in Figure 2 (g I and II) and Table 2 (g).

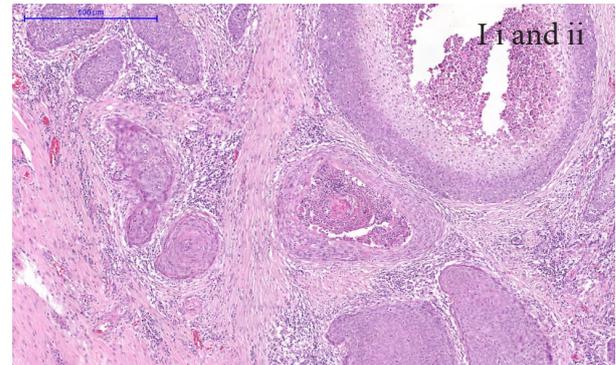
Example 5: The incisional biopsy in this case shows the presence of keratinized exophytic verruco-papillary processes with hyperplastic epithelium, however there is no prominent fibrovascular core indicative of squamous cell papilloma. There is absence of growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium and there is no frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium (producing pushing border effect) indicative of OVC as illustrated in Figure 2 (h) and Table 2 (h). There is also no frank invasion indicative of PSCC/CSCC, thus this case was diagnosed as OVH.

However, the excisional biopsy was diagnosed as papillary squamous cell carcinoma as there was the presence of frank invasion with cytological atypia as illustrated in Figure 2 (i) and Table 2 (i). Evethough there is exophytic papillary processes, CSCC was excluded as there was minimal keratinization.

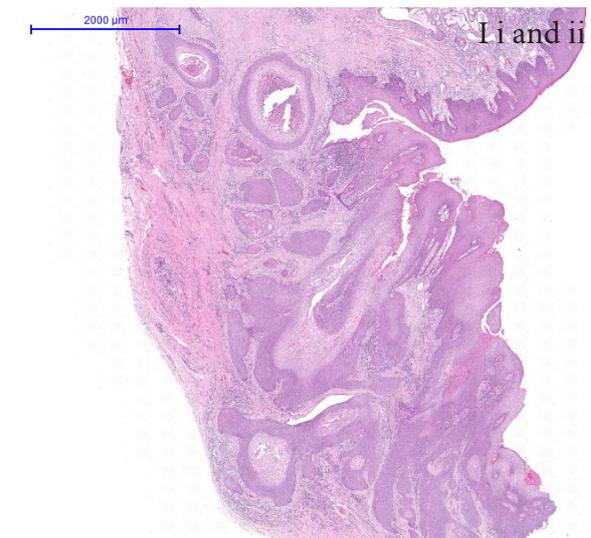
Examples 1, and 2 illustrate the accurate diagnosis of SCP and OVH as the incisional biopsies included the adjacent normal margins. Example 3 illustrates the use of OVH as a ‘holding diagnosis’ for either OVC or PSCC



**Figure 2. h): Example 5 - Photomicrograph of Oral verrucous hyperplasia at incisional biopsy**



**Figure 2. I i and ii): Example 5 - Photomicrograph of Papillary squamous cell carcinoma at excisional biopsy**



**Figure 2. I i and ii): Example 5 - Photomicrograph of Papillary squamous cell carcinoma at excisional biopsy**

**Table 2 (h): Description/Histological Criteria for Example 5 - Oral verrucous hyperplasia at incisional biopsy**

Description/Histological Criteria		
a	Keratinized exophytic verruco-papillary processes	Y
b	Epithelium is hyperplastic (basal cell hyperplasia and acanthosis)	Y
c	Growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium	N
d	Epithelial Dysplasia/cellular atypia	Y
e	Subepithelial lymphocytic infiltration	Y
f	Frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium showing pushing border effect	N
g	Prominent fibrovascular core	N
h	Invasion	N
i	Keratin plugging	Y
Y-Yes; N- No; UA – Unable to assess		

Diagnosis at incisional biopsy: Verrucous hyperplasia (presence of criteria a,b and absence of c). Other diagnosis excluded; 1) Squamous cell papilloma: Absence of histological criteria g and clinical size of >1cm 2) Verrucous Carcinoma: Absence of histological criteria f; 3) Papillary squamous cell carcinoma/Conventional squamous cell carcinoma with papillary features: Absence of histological criteria h

as there is an absence of adjacent normal margins in the incisional biopsy. Example 4 illustrates a situation whereby the incisional and excisional biopsies demonstrated a prominent keratinized exophytic component with focal areas exhibiting frank invasion. This was diagnosed as a conventional squamous cell carcinoma exhibiting a prominent exophytic papillary/verrucous component. Finally, example 5 illustrates a situation whereby the incisional biopsy had adjacent normal margins and an

**Table 2 (i): Description/Histological Criteria for Example 5 - Papillary squamous cell carcinoma at excisional biopsy**

Description/Histological Criteria		
a	Keratinized exophytic verruco-papillary processes (*minimal keratinization)	Y*
b	Epithelium is hyperplastic (basal cell hyperplasia and acanthosis)	Y
c	Growth of the hyperplastic epithelium into the lamina propria when compared with the level of the basement membrane of the adjacent normal epithelium	Y
d	Epithelial Dysplasia/cellular atypia	Y
e	Subepithelial lymphocytic infiltration	Y
f	Frank downward growth of the epithelial processes below the level of basement membrane of the adjacent normal epithelium showing pushing border effect	N
g	Prominent fibrovascular core	Y
h	Invasion	Y
i	Keratin plugging	N
Y-Yes; N- No; UA – Unable to assess		

Diagnosis at excisional biopsy: Papillary squamous cell carcinoma (presence of criteria a [with minimal keratinization], c g and h

OVH was diagnosed based on the set criteria. However, upon evaluating the surgical specimen, this was diagnosed as a PSCC. This further illustrates the need to excise and sample the whole specimen as there may be areas of PSCC in an OVH that may have been missed at incisional biopsy due to the biopsy site chosen.

Diagnostic challenges arose in clinically diagnosing and differentiating OVH, OVC and PSCC in situations where especially incisional biopsies lacked adjacent normal margins. Utilizing microsatellite analysis, Poh et al., (2001) found that the LOH pattern of OVH and OVC was sharply different from reactive hyperplasias (Poh et al., 2001). Thus, it was further suggested that microsatellite analysis may be useful in differentiating OVH/OVC from reactive epithelial hyperplasias to avoid repeated biopsies in difficult diagnostic situations. Distinguishing OVH from OVC may also pose diagnostic difficulties with absent normal margins. Klieb and Raphael, (2007) tried to address this issue through the utilization of an immunohistochemical panel of p53, matrix metalloproteinase-1, E-cadherin and Ki-67 to differentiate between OVC and OVH. They concluded that the pattern of expression of these four markers may be helpful in differentiating OVC from OVH although there is a need for further validation towards the use of this IHC panel as diagnostic adjunct in difficult cases.

The diagnosis of SCP is mostly straightforward especially for those measuring < 1cm. However, there have also been reports that even though uncommon; SCP may be more than 1cm in size (Chi et al., 2008). Identification of HPV 6 and 11 using in-situ hybridization in SCP may be helpful in differentiating OVH/OVC from SCP.

Patil et al., (2015) used the consensus criteria for OVH to re-evaluate 188 verrucopapillary lesions from pathology archives of different centres in India. Out of this, 57 cases (30.3%) were reclassified into OVH. They further described dysplastic features being present in 68.5% of OVH. Thus, it was proposed that OVH (with its distinct clinicopathologic entity) in their Indian study population should be considered in the classification of oral potentially malignant disorders.

Etiologically, betel quid chewing and tobacco smoking have been shown to be risk factors for OVH (Wang et al., 2009). In addition, Hwang et al., (2012) had also shown that while the presence of HPV in oral papillary and verrucous lesions is low, the clinical outcome of HPV positive oral papillary and verrucous lesions are poor where the rate of malignant transformation was high in HPV infected cases (Hwang et al., 2012). Another report on malignant transformation of OVH was by Poh et al., (2001) where the high progression risk of OVH was explained by the findings of high-risk LOH profiles in OVH.

#### Summary and conclusion

The consensus report identifies and summarises the criteria for diagnosis of Oral Verrucous Hyperplasia. Since some features of OVH can also be present in OVC, PSCC and SCP, an attempt to illustrate their similarities and differences has been presented. This paper further

illustrates the use of these criteria in assisting in the diagnosis of OVH, OVC, PSCC and SCP.

This consensus report is intended to standardize the criteria for diagnosis of OVH and its interpretation for use in the Asian region. This set of consensus criteria will enable the clinicians and pathologists to uniformly interpret their pool of OVH cases and facilitate a better understanding of their actual potential for malignant behavior. This will determine the possibility for inclusion of OVH into the OPMD group. Proper follow-up data of these patients would allow for verifications of the actual behavior of OVH, thus making it possible for its placement into the OPMD group.

#### Acknowledgements

This project on the development of the consensus criteria for verrucous hyperplasia was partly supported by the High Impact Research Grant [UM.C/625/1/HIR/MOHE/DENT/24]. The authors thanked all national and international workshop participants for the input towards in this project and the staff of the Oral Cancer Research and Coordinating Centre (OCRCC), Faculty of Dentistry, University of Malaya for their assistance.

#### References

- Allon D, Kaplan I, Manor R, et al (2002). Carcinoma cuniculatum of the jaw: a rare variant of oral carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, **94**, 601-8.
- Batsakis JG, Suarez P, El-Naggar AK (1999). Proliferative verrucous leukoplakia and its related lesions. *Oral oncology*, **35**, 354-9.
- Brown SM, Freeman RG (1976). Epithelioma cuniculatum. *Archives Dermatol*, **112**, 1295-6.
- Burkhardt A (1986). [Verrucous carcinoma and carcinoma cuniculatum--forms of squamous cell carcinoma?]. *Hautarzt*, **37**, 373-83.
- Chen PC-H, Chin-Chen P, Kuo C, et al (2006). Risk of oral nonmalignant lesions associated with human papillomavirus infection, betel quid chewing, and cigarette smoking in Taiwan: an integrated molecular and epidemiologic study. *Arch Pathol Lab Med*, **130**, 57.
- Chi AC, Damm DD, Neville BW, et al 2008. Oral and maxillofacial pathology, Elsevier Health Sciences.
- Ferlito A, Rinaldo A, Devaney KO, et al (1999). Papillary squamous cell carcinoma versus verrucous squamous cell carcinoma of the head and neck. *Ann Otol Rhinol Laryngol*, **108**, 318-22.
- Hansen LS, Olson JA, Silverman S (1985). Proliferative verrucous leukoplakia: a long-term study of thirty patients. *Oral Surg Oral Med Oral Pathol*, **60**, 285-98.
- Hwang CF, Huang CC, Chien CY, et al (2012). Human papillomavirus infection in oral papillary and verrucous lesions is a prognostic indicator of malignant transformation. *Cancer Epidemiol*, **36**, 122-7.
- Jacobson J, Van Dis M, Zakrzewska JM, et al (1996). Proliferative verrucous leukoplakia: a report of ten cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, **82**, 396-401.
- Jo VY, Mills SE, Stoler MH, et al (2009). Papillary squamous cell carcinoma of the head and neck: frequent association with human papillomavirus infection and invasive carcinoma. *Am J Surg Pathol*, **33**, 1720-4.
- Kallarakkal TG, Ramanathan A, Zain RB (2013). Verrucous

- papillary lesions: dilemmas in diagnosis and terminology. International journal of dentistry, 2013.
- Klanrit P, Sperandio M, Brown A, et al (2007). DNA ploidy in proliferative verrucous leukoplakia. *Oral Oncol*, **43**, 310-6.
- Klieb HBE, Raphael SJ (2007). Comparative study of the expression of p53, Ki67, E-cadherin and MMP-1 in verrucous hyperplasia and verrucous carcinoma of the oral cavity. *Head Neck Pathol*, **1**, 118-22.
- Koch BB, Trask DK, Hoffman HT, et al (2001). National survey of head and neck verrucous carcinoma. *Cancer*, **92**, 110-20.
- Poh CF, Zhang L, Lam WL, et al (2001). A high frequency of allelic loss in oral verrucous lesions may explain malignant risk. *Laboratory Investigation*, **81**, 629-34.
- Russell JO, Hoschar AP, Scharpf J (2011). Papillary squamous cell carcinoma of the head and neck: a clinicopathologic series. *Am J Otolaryngol*, **32**, 557-63.
- Schrader M, Laberke H (1988). Differential diagnosis of verrucous carcinoma in the oral cavity and larynx. *J Laryngol Otol*, **102**, 700-3.
- Shear M, Pindborg J (1980). Verrucous hyperplasia of the oral mucosa. *Cancer*, **46**, 1855-62.
- Slootweg PJ, Müller H (1983). Verrucous hyperplasia or verrucous carcinoma: an analysis of 27 patients. *J Maxillofacial Surg*, **11**, 13-9.
- Suarez PA, Adler-Storhiz K, Luna MA, et al (2000). Papillary squamous cell carcinomas of the upper aerodigestive tract: a clinicopathologic and molecular study. *Head Neck*, **22**, 360-8.
- Thomas GJ, Barrett AW (2009). Papillary and verrucous lesions of the oral mucosa. *Diagnostic Histopathol*, **15**, 279-85.
- Thompson LD, Wenig BM, Heffner DK, et al (1999). Exophytic and papillary squamous cell carcinomas of the larynx: a clinicopathologic series of 104 cases. *Otolaryngol-Head Neck Surgery*, **120**, 718-24.
- Wang YP, Chen HM, Kuo RC, et al (2009). Oral verrucous hyperplasia: histologic classification, prognosis, and clinical implications. *J Oral Pathol Med*, **38**, 651-6.
- Woo S-B, Grammer RL, Lerman MA (2014). Keratosis of unknown significance and leukoplakia: a preliminary study. *Oral Surg Oral Med Oral Pathol Oral Radiol*, **118**, 713-24.
- Yeh CJ (2003). Treatment of verrucous hyperplasia and verrucous carcinoma by shave excision and simple cryosurgery. *Int J Oral Maxillofac Surg*, **32**, 280-3.
- Zain R.B. KTG, Ramanathan A., Kim J., et al (2013). A Consensus report from the first asian regional meeting on the terminology and criteria for verruco-papillary lesions of the oral cavity held In Kuala Lumpur, Malaysia, December 15-18, 2013. *Ann Dentistry University Malaya*, **20**, 1-3.