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CASE REPORT

Verrucous Hyperplasia
Case report and differential diagnosis

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فرط التنسج الثؤلولي
تقرير حالة والتشخيص التفريقي

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ABSTRACT: Verrucous hyperplasia (VH) is a rare exophytic oral mucosal lesion which can transform into verrucous carcinoma (VC), its malignant but clinically similar counterpart. These entities can be distinguished by the lack of invasive growth in VH cases; as such, it is essential to include a margin with adequate depth when performing a biopsy of the epithelium of the lesion. We report an 80-year-old male patient who presented to the Bapuji Dental College & Hospital, Davangere, Karanataka, India, in 2011 with a warty whitish-pink growth on the inside of his cheek. The patient was treated with wide surgical excision of the lesion and a diagnosis of VH was made based on histopathological features. There was no evidence of recurrence at a five-year follow-up. This report highlights the histological variations, pathogenesis and differential diagnosis of VH.

Keywords: Hyperplasia; Verrucous Carcinoma; Squamous Cell Carcinoma; Histology, diagnosis; Case Report; India.

الملخص: فرط التنسج الثؤلولي هو آفة غير شائعة لمخاطية الفم خارجية التنبت والتي قد تتحول إلى سرطان ثؤلولي، وهي خبيثة ولكنها مشابهة إكلينكيا للآفة المقابلة. هذة الكيانات تفرق بعدم القدرة على النمو الغزوي في حالات فرط التنسج الثؤلولي، لذا، من الأساسيات عند أخذ خزعة من ظهارة الآفة أن تشمل على هامش ذو عمق مناسب. نعرض هنا حالة لمريض ذكر عمرة 80 عاما تقدم إلى كلية ومستشفى بابجي لطب الأسنان، دافانجري، كارنتكا، الهند في عام 2011 بورم ثؤلولي أبيض زهري في الجزء الداخلي للخد. تم علاج المريض باستئصال جراحي واسع للآفة وتم تشخيص الحالة بفرط التنسج الثؤلولي بناءا على ملامح مرضيات الأنسجة. لا يوجد أي دليل على تجدد حدوث الآفة خلال فترة الخمسة سنوات للمتابعة. هذا التقرير يسلط الضوء على اختلافات مرضيات الأنسجة، الإمراض والتشخيص التفريقي لفرط التنسج الثؤلولي.

الكلمات المفتاحية: فرط التنسج؛ سرطانة ثؤلولية؛ سرطانة حرشفية الخلايا؛ علم الأنسجة، التشخيص؛ تقرير حالة؛ الهند.

Verrucous hyperplasia (VH) is a pre-malignant exophytic oral mucosal lesion with a predominantly verrucous or papillary surface; this lesion can subsequently transform into verrucous carcinoma (VC), a well-established warty variant of squamous cell carcinoma (SCC).[1] Among 324 Taiwanese patients, Hsue *et al.* found the malignant potential of VH to be 3.1% over an average of 54.6 months.[2] As VH and VC may present with similar clinical features, these entities need to be distinguished histologically. In 1980, Shear *et al.* first differentiated VH from VC based on the absence of endophytic growth in the former entity, wherein the verrucous and hyperplastic epithelium was completely superficial to the adjacent normal epithelium.[3] Therefore, it is crucial that biopsies of verrucous lesions include a lesional margin with adequate depth.

Case Report

An 80-year-old male patient presented to the Outpatient Department of the Bapuji Dental College & Hospital, Davangere, Karanataka, India, in 2011 with a growth on the inside of his cheek. Six months prior to presentation, the patient had noticed a pea-sized growth in his mouth which had continued to grow over time. He did not report any pain associated with the growth unless he accidentally bit it whilst chewing food. Although the patient had not smoked or chewed tobacco for the previous 7–8 years, he reported a prior 40-year history of chewing tobacco 3–4 times per day and smoking 2–4 *bidis* (i.e. thin Indian cigarettes made of unprocessed tobacco wrapped in leaves) per day.

On clinical examination, a whitish-pink sessile oral mass of approximately 1.5 x 1.5 cm was observed with

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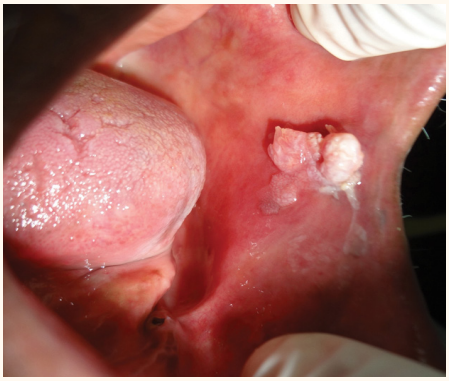

Figure 1: Intraoral photograph showing a whitish-pink sessile exophytic lesion on the buccal mucosa of an 80-year-old male patient.

a warty/pebbly superficial surface and clearly defined margins [Figure 1]. It was firm in consistency and non-tender upon palpation. There was no evidence of discharge and no ulcerations were observed on the surface of the lesion, nor in the surrounding mucosa which appeared normal. An extraoral examination revealed an enlarged submandibular lymph node, which was mobile and non-tender upon palpation.

The lesion was treated with wide surgical excision. Histopathological examination of a biopsy specimen revealed a hyperplastic stratified squamous epithelium arranged in the form of exophytic papillary projections, with underlying fibrovascular connective tissue [Figure 2A]. The epithelium exhibited hyperparakeratinisation with a few koilocytes seen in the superficial layers. The rete ridges had a broad 'elephant's foot' shape and were at the same level as that of the adjoining normal epithelium [Figure 2B]. Some of the cells in the basal layer of the epithelium exhibited dysplastic features. In addition, the underlying connective tissue revealed dense chronic inflammatory cell infiltrates, chiefly concentrated in the juxta-epithelial areas. As a result of these features, a final diagnosis of VH was made. The patient was subsequently followed-up periodically over the next five years with no sign of recurrence [Figure 3].

Discussion

Clinically, VH presents as a warty or papillary fungating exophytic mucosal mass which can sometimes ulcerate and is predominantly pink in colour with a partly whitish surface.[4] The average age at first presentation is between 30–60 years old.[4,5] Previous research has indicated the buccal mucosa to be the most common site for VH; this may potentially be correlated with usage of *quid* (i.e. clumps of chewing tobacco) which is usually placed in this region of the mouth.[5,6] In contrast, Shear *et al.* found that the *gingiva* and alveolar mucosa were the most common sites among 68 cases of VH.[3] Hazarey *et al.* reported that placement of tobacco-*betel*-lime *quid* (i.e. a mixture of slaked lime, chewing tobacco and *betel* leaf pieces) in the buccal vestibule was the most predominant habit associated with VH growth.[6] Wang *et al.* similarly observed that 91% of 60 patients with VH chewed *areca* nut *quid* (i.e. a mixture of *areca* nut, *betel* leaf pieces and chewing tobacco).[5] Smoking was reported to be the second most common aetiological factor in these two studies.[5,6]

Shear *et al.* classified two histological patterns of VH, including the "sharp" variety (comprised of heavily keratinised, long and narrow verrucous processes) and the "blunt" variety (comprised of less heavily keratinised, broader and flatter verrucous processes).[3] The former may potentially be referred to as verrucous leukoplakia due to its predominantly white colour resulting from the heavy keratinisation.[3] However, no difference in prognosis has been reported according to these patterns. In contrast, Wang *et al.* classified VH into plaque-type and mass-type lesions and identified significant differences in their malignant transformation rates.[5] Plaque-type VH was defined as horizontally-proliferating epithelial hyperplasia resulting in an elevated plaque-like lesion with a verrucous surface, while mass-type VH lesions displayed single or multiple protuberant masses of

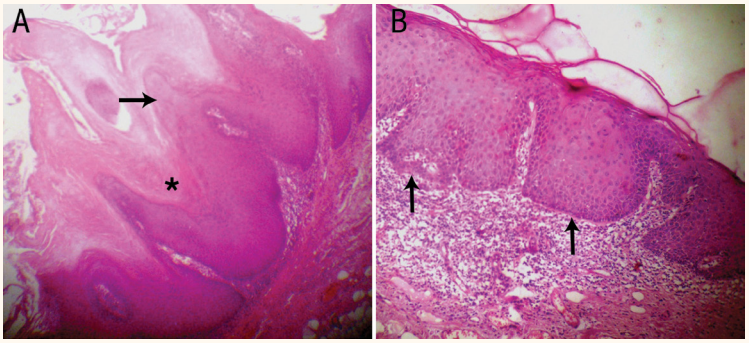

Figure 2: Photomicrographs of haematoxylin and eosin stains at x100 magnification showing (**A**) papillary projections (arrow) with keratin plugging (asterisk) in the clefts and (**B**) broad 'elephant's foot' rete ridges (arrows) at the same level as that of the adjacent normal epithelium.

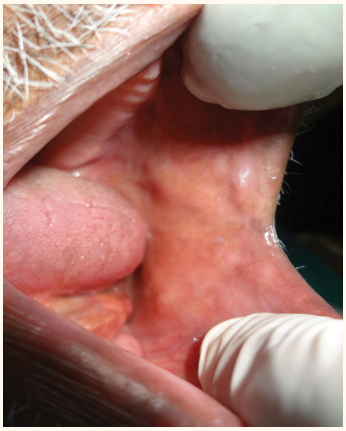

Figure 3: Intraoral photograph of the buccal mucosa of an 85-year-old male patient showing no evidence of recurrence of verrucous hyperplasia five years after wide surgical excision of the lesion.

epithelial hyperplasia, with very little connective tissue at the core and a verrucous surface.[5]

Histopathologically, all variants of VH exhibit verrucous projections of the hyperplastic epithelium which lie superficially to the adjacent epithelium.[3,5] However, there are considerable similarities between VH and VC lesions. The latter is defined as a warty, papillary or fungating exophytic lesion with broad and intact intrusions of rete ridges.[3] According to previous research, keratin plugging in the centre of epithelial invaginations is a histological hallmark of VC; however, Slootweg *et al.* reported that the presence of keratin plugging is not obligatory for a VC diagnosis.[4,7] Although dysplasia is rarely seen, mitotic figures are more common.[4] The distinction between VH and VC is histological, based on the location of the hyperplastic epithelium in relation

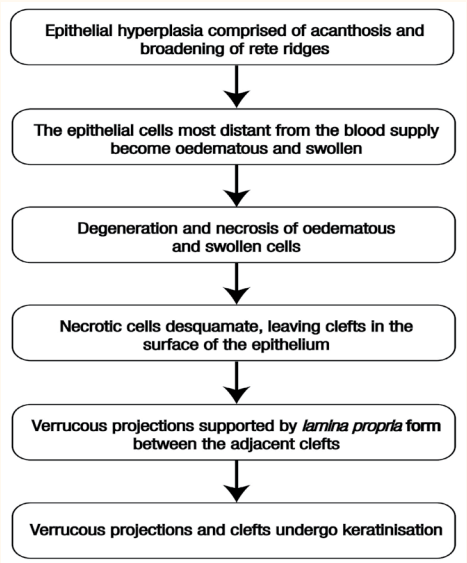

Figure 4: Flowchart depicting the histogenesis of verrucous hyperplasia as proposed by Shear *et al.*[3]

Table 1: Clinicopathological spectrum of verrucous lesions[8]

Grade	Entity	Histopathological features
0	None	Normal oral mucosa
2	Clinical leukoplakia	Hyperkeratosis with or without dysplasia
4	Verrucous hyperplasia	Leukoplakia with papillary exophytic proliferation of the epithelium
6	Verrucous carcinoma	Downgrowth of the well-differentiated squamous epithelial blunt rete ridges with intact basement membrane
8	Papillary carcinoma	Exophytic and invasive growth of the well-differentiated squamous epithelium with keratin formation and minimal dysplasia
10	SCC	Loss of cohesion of moderately/poorly-differentiated tumour cells with moderate to severe dysplasia and minimal keratin formation

SCC = squamous cell carcinoma.

to the adjacent normal epithelium; furthermore, the broadened epithelial ridges lie above the adjacent normal epithelium in VH, whereas similar rete ridges display an endophytic growth pattern in VC cases.[6] In addition, the verrucous processes in VC often bring a margin of normal epithelium down with them into the underlying connective tissue.[3]

The histogenesis of VH as proposed by Shear *et al.* is summarised in Figure 4.[3] It has been proposed that leukoplakia, if left untreated, may transform into VH or VC over time.[3] Moreover, VH can be confused with proliferative verrucous leukoplakia (PVL), a variant of non-homogenous leukoplakia in which the lesions eventually assume an exophytic verrucous appearance.[8] While the term VH refers to both clinical and histopathological features, PVL is unequivocally accepted as a clinical term used to define a specific type of non-homogenous leukoplakia with a verrucous surface.[4] Histologically, PVL displays clinical *foci* of hyperkeratosis that progressively spread and become multifocal. Many cases of PVL are extremely resistant to treatment and progress to invasive cancer.[8] In cases of papillary squamous cell carcinoma (PSCC), VC can be distinguished by its intact basement membrane which contrasts with the focal or early invasion seen in PSCC; furthermore, the epithelium in PSCC cases is significantly dysplastic when compared with the almost 'bland' cytological features of the epithelium of VC lesions.[9] The clinicopathological spectrum of verrucous lesions as proposed by Hansen *et al.* is shown in Table 1.[8]

The malignant potential of VH is well established.[1–3] Slootweg *et al.* concluded that VH probably

represents a morphological variant of VC after noting an association between VH and SCC in 37% of 27 patients.[4] Chen *et al*. reported high expression of inducible nitric oxide synthase (iNOS) proteins and messenger ribonucleic acid in VH lesions and concluded that an iNOS-dependent mechanism may be involved in the malignant transformation of VH.[10,11] Additionally, the higher expression of interleukin-1β and glutathione S-transferase pi isoenzymes and the allelic loss at 19 *loci* on seven different chromosome arms may also play an important role in the malignant transformation of VH.[12–14] Tumour protein p53, epidermal growth factor receptor and human epidermal growth factor receptor 3 expression can also be used to differentiate VH from VC and SCC.[15,16] Although Greer Jr *et al*. found an association between the human papilloma virus and VH, the role of the virus in the malignant transformation of VH has yet to be confirmed.[17]

In terms of treatment modality, surgery alone is the most common method of management for both VC and VH cases, due to their overlapping clinicopathological features.[18,19] However, it is important to ensure wide surgical excision of the lesion with adequate soft tissue margins so as to avoid recurrence. Although sporadic cases of cervical and distant metastasis have been reported, the overall rate of metastasis is insignificant.[20] An incorrect histological diagnosis or the presence of occult *foci* indicating SCC has been proposed to justify the metastatic nature of lesions otherwise characteristic of VC; as such, thorough sampling of the surgical specimen is highly recommended.[20,21]

Conclusion

Distinction between VC and VH lesions can only be made histologically, by comparing the level of the rete ridges of the epithelium of the lesion with that of the adjacent normal epithelium. In addition, VH cases may also be confused with verrucous leukoplakia. Thus, biopsies of verrucous lesions should include the adjacent normal epithelium in order to ensure correct diagnosis. As VH has the potential for malignant transformation, patients should be treated in a similar manner to those with VC.

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