Verrucous Hyperplasia – Case Series: A Diagnostic Dilemma

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Abstract

Verrucous hyperplasia (VH) and verrucous carcinoma (VC) are two distinct clinicopathologic verrucous entities. However, the clinical distinction between the two lesions still remains enigmatic. Hence, the histopathological characteristics of both VH and VC being distinguished from each other by an exophytic and endophytic growth pattern, respectively, remain the gold standard in the diagnosis and further management.

Keywords: Epithelial dysplasia, Proliferative verrucous leukoplakia, Squamous cell carcinoma, Verrucous carcinoma.

Introduction

Verrucous hyperplasia (VH) is a potentially 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] oral VH might be a precursor in the development oral VC due to the astonishing resemblance between them.[2] Oral VC is a rare variant of oral SCC, first described by Ackermann and, henceforth, also known as Ackermann's tumor.[3]

VH and VC often coexist with dysplasia and have been reported to progress into SCC.[4] VC has unique histopathologic features, and hence, diagnosis is challenging for the clinicians. For accurate evaluation, an adequate biopsy sample is of utmost importance along with a multidisciplinary interaction between the clinician and the pathologist. In fact, some studies have reported that it takes an average of three to four biopsies to formulate an accurate diagnosis of both VH and VC.[5] Shear and Pindborg described the histopathological diagnostic criteria to differentiate between these two verrucous lesions. In the former, the verrucous processes and the greater part of the hyperplastic epithelium are superficial to adjacent normal epithelium than the latter wherein verrucous processes are superficial, but the broad rete processes extend considerably deeper than adjacent normal epithelium, often pulling a margin of normal epithelium down with them into the underlying connective tissue.[4]

The histological criteria for the diagnosis of oral VC included: (a) Epithelial overgrowth with wide and elongated rete ridges exhibiting a pushing border invasion into the underlying connective tissue, (b) papillary or verruciform epithelial projections with abundant parakeratin production, and (c) the lesional epithelial cells showing a normal maturation pattern with no significant degree of cellular atypia. On the contrary, histological criteria employed for the diagnosis of oral VH are: (a) Epithelial hyperplasia with parakeratosis or hyperkeratosis and verrucous surface and (b) no invasion of the hyperplastic epithelium into the lamina propria compared with adjacent normal mucosal epithelium.[6]

Therefore, the VH is best distinguished from VC in histopathologic sections taken from the margins of the lesions.

Case Series

Five cases of histopathologically diagnosed VH (Figure 1) from the year 2019 to 2021 have been retrieved from the archives of the department of oral pathology and microbiology. Clinical and histopathological observations are summarized in Table 1.

Discussion

Clinically, VH presents as a warty or papillary exophytic mucosal mass which is predominantly pink in color with a partly whitish

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Table 1: Clinical and histopathological features of verrucous hyperplasia in cases

S. No.	Age/ sex	Site	Type of biopsy	Appearance of lesion	Histopathological features	Histopathological diagnosis
1	60/F	Left buccal mucosa	Punch biopsy	Diffuse, white, erythematous, cauliflower like growth	Hyperkeratotic proliferative squamous epithelium and minimal connective tissue. Epithelium revealed dysplastic features.	Verrucous hyperplasia with moderate dysplasia
2	60/M	Lower front region	Incisional biopsy	White patches and deep furrow were present	Hyperkeratotic proliferative squamous epithelium and minimal connective tissue. Epithelium revealed dysplastic features such as basal cell hyperplasia, cellular and nuclear pleomorphism, mitotic figures, individual cell keratinization, and loss of basement membrane in few areas	Verrucous hyperplasia with moderate dysplasia
3	42/M	Lower right vestibule	Incisional biopsy	Diffuse, white keratotic exophytic growth on lower right vestibule	Hyperplastic, hyperkeratinized stratified squamous epithelium connective tissue was inflamed and vascular. Epithelium revealed dysplastic features up to two-third level.	Verrucous hyperplasia with moderate dysplasia.
4	63/M	Lower front vestibule	Excisional biopsy	Whitish, velvety appearance seen on the lower front vestibule	Hyperkeratotic stratified squamous epithelium. Epithelium revealed dysplastic features.	Verrucous hyperplasia with severe dysplasia
5	82/M	Right lower alveolus	Both incisional and excisional biopsy was done	White exophytic growth in the right lower alveolus	Hyperkeratotic stratified squamous epithelium and connective tissue stroma. Epithelium revealed dysplastic features	Verrucous hyperplasia with severe dysplasia

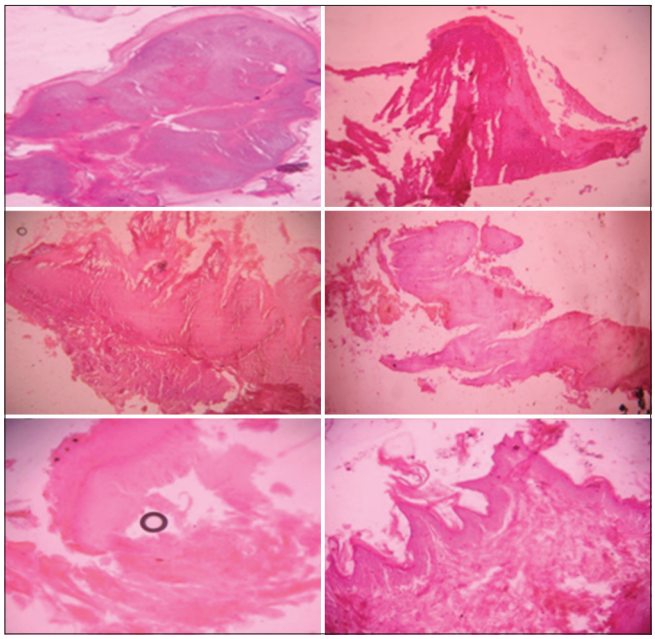

Figure 1: Histopathological features of verrucous hyperplasia in cases

surface which can sometimes ulcerate.[7] In the present cases, the common age of presentation was between 40 and 60 years which is similar to the age of occurrence proposed by Slootweg and Müller.[7,8] Hazarey et al. reported that the 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 the occurrence of such verrucous growth.[9] Wang *et al*. similarly observed that 91% of 60 patients with VH chewed areca nut quid.[8]

Shear *et al.* classified two histological patterns of VH, including the "sharp" variety (having heavily keratinized, long and narrow verrucous processes) and the "blunt" variety (comprising of less heavily keratinized, broader and flatter verrucous processes). The former may potentially be referred to as verrucous leukoplakia due to its predominantly white color resulting from the heavy keratinization.[4]

Histopathologically, all variants of VH exhibit verrucous projections of the hyperplastic epithelium which lie superficially to the adjacent epithelium. However, there are considerable similarities between VH and VC lesions. The previous studies reported keratin plugging in the center of epithelial invaginations is a histological hallmark of VC. However, Slootweg and Müller reported that the presence of keratin plugging is not obligatory for VC diagnosis.[10]

The distinction between VH and VC is histopathological and is based on the location of the hyperplastic epithelium in relation to the adjacent normal epithelium; furthermore, the broadened epithelial ridges lie above the adjacent normal epithelium in VH. Similarly, 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. 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. Histologically, PVL displays clinical foci of hyperkeratosis that progressively spreads and becomes multifocal. Many cases of PVL are extremely resistant to treatment and progress to invasive cancer.[11]

The malignant potential of VH is well established.[12] Chen et al. reported high expression of inducible nitric oxide synthase (iNOS) proteins and messenger ribonucleic acid

in such lesions and concluded that an iNOS-dependent mechanism may be involved in the malignant transformation of VH.[10,13] 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.[14] Tumor 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]

VH has been considered an antecedent stage or early form of VC and is believed to have the same biological potential. Surgery has been the first choice of treatment for these lesions, and radiotherapy is controversial surgery combined with radiotherapy which is the next most preferable treatment and may have benefits, particularly in cases of extensive lesions. Recurrence rate is high in cases in which either irradiation or surgery alone is performed.[16,17] However, it is important to ensure wide surgical excision of the lesion with adequate soft-tissue margins so as to avoid recurrence.

Conclusion

VH and VC are closely mimicking lesions that are difficult to clinically diagnose. Hence, histopathological evaluation plays a key role in establishing a diagnosis. Cytological atypia, associated with epithelial dysplasia, has been often identified as a significant related feature in VH and estimated malignant transformation rate is about 20%. It should be kept in mind that VH may transform into VC. Hence, VC acts as a potentially malignant disorder. Therefore, patients must be treated aggressively with regular follow-up.

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Conflicts of interest

There are no conflicts of interest.

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