Papillary and verrucous lesions of the oral mucosa

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Abstract
A variety of verrucous and papillary lesions affect the oral mucosa. Those which are benign and reactive, for example squamous papilloma or verruciform xanthoma, usually present little diagnostic difficulty. However, dysplastic and malignant verrucous and papillary lesions are a much greater diagnostic challenge, not helped by confusing terminology. Papillary hyperplasia is a reactive inflammatory condition, whereas verrucous hyperplasia is a potentially malignant dysplasia, and probably part of the spectrum of verrucous carcinoma. Papillary carcinomas, at least in the oral context, are essentially verrucous hyperplasias. ‘Oral florid papillomatosis’ is an obsolete term synonymous with verrucous carcinoma. A ‘classical’ verrucous carcinoma, with an exo-/endo-phytic growth pattern, ‘pushing’ invasive front and intact basement membrane, is easily identified, but many exophytic verrucous hyperplasias also show endophytic growth. These can also reasonably be diagnosed as verrucous carcinoma. If the lesion shows more than focal, early invasive disruption of the basement membrane, it should be diagnosed as a conventional squamous cell carcinoma.

Keywords papillary carcinoma; precancerous conditions; verrucous carcinoma

Introduction
There are few more diagnostically challenging areas of oral pathology than papillary and verrucous lesions. Not only is the terminology confusing (Table 1), but some normal oral mucosal structures, inflammatory polyps and viral papillomas as well as dysplastic and malignant lesions may share microscopic appearances. Clinical information and an adequate biopsy are essential for accurate diagnosis. The purpose of this review is to highlight the histological features which provide guidance in the assessment of this difficult group of lesions, paying particular attention to verrucous hyperplasia, papillary dysplasia, papillary and verrucous carcinoma.

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Table 1

Normal papillary structures of the lingual mucosa
Covering the entire anterior two-thirds of the dorsum of the tongue are filiform papillae with parakeratinized surface projections and a prominent granular layer. The latter in particular can be reminiscent of that seen in viral papillomas. Filiform papillae are characteristically lost in disease processes such as geographical tongue (erythema migrans), lichenoid reactions, chronic candidal infection or chronic anaemia. Fungiform papillae, which are mushroom-shaped structures bearing scattered, paler staining taste buds within the surface stratified squamous epithelium, are located along the lateral aspects of the tongue dorsum. These may persist in conditions where the filiform papillae are lost, and thus appear more prominent. The circumvallate papillae are located at the junction of the anterior two-thirds with the posterior one-third of the tongue and are approximately 12 in number. They are surrounded by a ‘ditch’, lined by stratified squamous epithelium containing many taste buds, which leads to the serous minor salivary glands (of von Ebner) embedded within the lingual musculature.

Viral papillomas
These comprise squamous papilloma (which make up the vast majority), verruca vulgaris and condyloma acuminatum. Diagnosis is usually straightforward; most are less than 10 mm in
maximum dimension and the histopathological features are more or less those of lesions occurring on the skin.

Squamous papillomas may affect any intra-oral site. The length and number of fronds is variable; indeed, many papillomas lack them and show a broad, papillonodular surface morphology. Should the dorsum of the tongue be affected, the fronds are usually longer than adjacent filiform papillae. Viral cytological changes are minimal. Squamous papillomas are frequently inflamed and in about 10% of them candidal hyphae can be demonstrated with PAS stains.1 Verruca vulgaris affects the lips in more than half of cases, the palate being the commonest intra-oral site.2 They may appear histologically identical to squamous papilloma, but features of human papillomavirus (HPV) infection, such as hypergranulosis, apparent keratinocyte atypia, ‘mitosoid’ cells or bodies (keratinocytes with coarse, clumped chromatin with a pattern resembling a mitotic spindle), perinuclear haloes and koilocytic change are evident. Flat-ter condylomas also affect the lips more often than intra-oral sites, and may also demonstrate the cytological features of viral infection listed above.

Focal epithelial hyperplasia in the UK is rare, and is due to infection with HPV types 13 and 32. It usually affects younger patients and manifests as multiple mucosal nodules, which may look like fibro-epithelial polyps both clinically and histologically. None of the viral papillomas carries any pre malignant connotation.

Reactive verrucous and papillo-nodular lesions

Fibro-epithelial polyps
These rarely cause any diagnostic difficulty, but lesions affecting the tip of the tongue in particular may have a striking papillonodular morphology.

Smoking-induced hyperkeratosis
These may have a ‘chevron’ papillary surface pattern (Figure 1). Another clue to a smoking-associated lesion is hypermelanosis in the basal and parabasal strata, with associated pigmentary incontinence in the juxta-epithelial lamina propria.

Verruciform xanthoma
The mouth, in particular the gingiva, alveolar ridge and palate, is the commonest site for these rare, but easily diagnosed reactive lesions which present as solitary nodules. Any age, but particularly the fifth to seventh decades, may be affected and there is a more-or-less equal sex incidence. The clinical presentation is of a solitary, discrete nodule which is usually painless, about 1 cm in size, and either sessile or pedunculated. HPV infection is not implicated in the aetiology, which remains unknown. Histologically verruciform xanthomas have defined borders peripherally and deeply, and an exophytic growth pattern. The surface stratified squamous epithelium, though often verrucous, can be composed of flat-topped papillae (Figure 2a) covered by a thickened layer of parakeratin which has a tendency to stain orange with H&E. There are also broad, hyperplastic rete ridges between which are keratin plugs. Superficial micro-abscesses may be associated with candidal infection (Figure 2b). Characteristically, however, the connective tissue papillae are filled with foamy histiocytes which express macrophage markers (Figure 2b). Occasional xanthoma cells may appear within the epithelium or deeper connective tissue. Touton giant cells are absent and there are no systemic implications.

Figure 1
Biopsy from the cheek mucosa showing a ‘chevron’ papillary surface pattern of a smoking-related hyperkeratosis.

Figure 2
a Verruciform xanthoma showing spikes of parakeratin and flat-topped papillae, with deep clefts filled with keratin. b At higher power, there is hyperparakeratinization and connective tissue papillae which are filled with xanthoma cells. Superficial abscesses suggest the presence of candidal infection.
Papillary hyperplasia

This is another reactive hyperplasia which most commonly, though by no means invariably, affects the palatal mucosa supporting a denture. However, the lesion does not necessarily resolve following correction of any prosthetic problem, some patients affected by papillary hyperplasia do not wear dentures and non-denture bearing sites may be affected (Figure 3). Histologically there are multiple papillary projections of hyperplastic epithelium, each with a vascular connective tissue core. Diagnostic difficulty is usually the result of an inadequate or poorly orientated biopsy, which may give rise to a pseudocarcinomatous appearance. Candidal infection is typical, but again not inevitable, and the lesion may persist after antifungal therapy. The lamina propria is often chronically inflamed. In contrast to verrucous hyperplasia (see below), there is no potentially malignant connotation with papillary hyperplasia. Nevertheless, a period of follow-up and antifungal treatment where necessary are usually recommended.

Verrucous hyperplasia, papillary dysplasia, papillary and verrucous carcinoma

The uncertainty as to the true nature of these lesions is betrayed by the morass of confusing and unsatisfactory terminology. As described above, papillary hyperplasia is a reactive condition, whereas verrucous hyperplasia is, at best, a potentially malignant dysplasia, if not a carcinoma in situ or indeed a frank malignancy.

Ackerman, in the first description of the entity, showed that verrucous carcinoma has the potential to destroy neighbouring tissues (including bone). He had no doubt that verrucous carcinoma is an overtly malignant process, yet many pathologists understandably balk at the concept of such a lesion being classed as malignant where there is no conventional disruption of the basement membrane. Having labelled the entity a carcinoma, it may then be difficult for the pathologist to convey the message that, though malignant, there is minimal metastatic potential and that further treatment may not be necessary if the entire lesion has been excised and examined microscopically. ‘Verrucous hyperkeratosis’ can be a useful descriptive term, histologically and clinically, but is not a defined entity like verrucous hyperplasia and verrucous carcinoma and its use as a ‘sign out’ diagnosis may lead to clinical confusion. ‘Verrucous leucoplakia’ is a purely clinical descriptive term which encompasses verrucous hyperplasia, verrucous carcinoma, conventional squamous cell carcinomas and indeed any lesion which presents as a verrucous or papillary white patch. It should not be issued as a pathological diagnosis.

Papillary dysplasia and papillary carcinoma are terms more traditionally applied to lesions of the larynx, and the World Health Organization (WHO) does not allocate a separate description to oral lesions in their latest fascicle. In the oral context, both the terms ‘papillary dysplasia’ and ‘papillary carcinoma’ essentially describe exophytic dysplasias generally lacking the ‘spiky’ hyperkeratosis of verrucous hyperplasia and verrucous carcinoma. However, as will become apparent in the ensuing discussion, the definition of verrucous hyperplasia would encompass most papillary dysplasias and carcinomas. Some pathologists might nevertheless regard papillary dysplasia or papillary carcinoma as a more appropriate label than verrucous hyperplasia for rare oral lesions. ‘Oral florid papillomatosis’ is a term synonymous with verrucous carcinoma which is nowadays seldom encountered in clinical or pathological practice, or the recent literature.

Verrucous carcinoma

In trying to elucidate an approach to the diagnosis of dysplastic and malignant verrucous lesions, it is perhaps as well to begin with verrucous carcinoma, since it is a well described entity and, in its ‘classical’ form, is the easiest member of this group of lesions to recognize. The mucosa of the cheek and gingiva (usually mandibular) are the sites most commonly affected, and the majority of patients (though by no means all) tend to be elderly and male. The characteristic histological features are those of a verrucous hyperkeratosis with an exo-/endo-phytic growth pattern.
The rete processes are cytologically bland, broad, elongated and widened, with a so-called ‘elephant’s foot’ appearance. Plugs of keratin may extend to the full depth of the rete ridges. There is a well demarcated, ‘pushing’ invasion front (Figure 4) and commonly a dense lymphoplasmacytic host response. A critical feature is the transition zone between normal and abnormal epithelium, which is abrupt, with downward retraction of the normal epithelium and deep extension of the abnormal rete ridges relative to the adjacent normal epithelium. Whilst this may or may not be the case with verrucous hyperplasias (see below), it is always the case with verrucous carcinomas. The presence of significant cytological dysplasia theoretically excludes a diagnosis of verrucous carcinoma, as would the lack of an endophytic growth pattern.

It is common to find oral squamous cell carcinomas, which are conventionally invasive at presentation, with areas where the surface could be described as verrucous or papillary. The use of terms such as ‘hybrid tumour’ serves no practical purpose, and anything more than minimal invasive disruption of the basement membrane, and certainly typical stromal invasion by islands of malignant epithelium, rules out a diagnosis of verrucous carcinoma; such a tumour behaves as a conventional squamous cell carcinoma and should be diagnosed and treated as such (Figure 5).

**Verrucous hyperplasia**

Shear and Pindborg are often credited with coining the term ‘verrucous hyperplasia’, but Ackerman and McGavran employed it more than 20 years previously to describe a precursor to verrucous carcinoma. Nevertheless, Shear and Pindborg were the first to perform a detailed histological analysis which attempted to discriminate between verrucous hyperplasia and verrucous carcinoma. They described two forms of verrucous hyperplasia, a ‘sharp’ variety with spiked, heavily keratinized processes, but with a lesser degree of keratin plugging (Figure 6), and a ‘blunt’ variant with broader, shorter, less or non-keratinized processes (Figure 7). ‘Verrucous hyperplasia’ is unsatisfactory as a histological diagnosis, since it does not convey the fact that 31–66% of such lesions are dysplastic. Clearly, therefore, a diagnosis of verrucous hyperplasia requires to be qualified with an assessment of the degree of dysplasia, though the grossly abnormal architectural changes of a verrucous hyperplasia are an argument for labelling all such lesions as at least moderate to severely dysplastic regardless of the extent of cytological atypia. Some authors regard verrucous hyperplasia as a morphological variant, or at least a precursor, of verrucous carcinoma. Therefore, which is the correct term to use and when?

**Verrucous hyperplasia or verrucous carcinoma?**

There are no clear clinical features which help distinguish the two lesions. The cheek mucosa is the commonest site for both, and similar age groups are affected. However, an interesting observation is that only 26% of verrucous hyperplasias affect sites where the mucosa is ‘tied down’ to bone, such as the gingiva and palate, compared to 53% of verrucous carcinomas, and it has been postulated that this accounts to some extent for their different growth patterns.

In practical terms, the main histological features used to distinguish between verrucous hyperplasia and verrucous carcinoma are growth pattern, rete morphology and the degree of cytological atypia. Verrucous hyperplasia is exophytic relative to the adjacent epithelium, and the hyperplastic rete processes are usually pointed, ragged, slender and anastomosing. In contrast, verrucous carcinoma has an exo- and endo-phytic growth pattern, with broad, elongated, rete processes which, as mentioned above, are said to resemble elephant’s feet in profile (see Figures 4 and 5). Marked cytological atypia is a feature of verrucous hyperplasia rather than verrucous carcinoma, although this is not prominent in the lesion illustrated in Figure 7. In some circumstances verrucous hyperplasia may act as a ‘holding’ diagnosis. For example, in one series, the term verrucous hyperplasia was used where a diagnosis of verrucous carcinoma was being considered, but could not be made because the infiltrative, pushing nature of the deep margin was not apparent, that is the biopsy was inadequate. If the term verrucous hyperplasia is used in this manner, the pathology report must make it clear that verrucous carcinoma is not being excluded and that a further, deeper sample is necessary for definitive diagnosis.

Unfortunately, even when a good biopsy is available, many lesions defy neat categorization. Slootweg and Muller reported that a quarter of the lesions they analysed could not easily be designated as either verrucous hyperplasia or verrucous carcinoma on microscopic grounds. Similarly, Shear and Pindborg found that 29% of verrucous hyperplasias also showed features of verrucous carcinoma, such as downward retraction of the adjacent normal epithelium and endophytic growth, with or without extension of abnormal epithelium into striated muscle.

Thus, Slootweg and Muller concluded that verrucous hyperplasia and verrucous carcinoma represented a spectrum of the same process, a view now held by many experts in the field. Even at the extremes of the spectrum the distinction is arguably academic; both lesions require complete excision, if possible, to allow analysis of the entire lesion, since 10–42% of verrucous hyperplasias and verrucous carcinomas either contain a frankly malignant, conventionally invasive focus when the whole lesion is examined microscopically, or go on to become invasive.
What, then, should an endophytic verrucous lesion showing invasion of deep structures, but lacking the ‘classical’ features of a verrucous carcinoma, be signed out as? At the risk of offending purists, verrucous carcinoma would seem to be an appropriate designation for such lesions. This conclusion is given credibility by photomicrographs in several papers by well respected authors, where verrucous hyperplasias (on the basis of the above criteria) and lesions lacking the ‘classical’ features of verrucous carcinomas are nevertheless all classified as the latter.

Crucially, the pathologist must ensure the correct message reaches the surgical team managing the patient, and that the clinicians concerned understand the concept of not only verrucous carcinoma and what it signifies, but also the possible progressive nature of verrucous hyperplasia. It should be emphasized that complete local excision of verrucous carcinoma is likely to be curative, with no necessity for neck dissection (unless there are other indications) at this juncture. It might be tempting to use terminology such as ‘well differentiated squamous cell carcinoma’. 

**Figure 6**

‘Sharp’ verrucous hyperplasia with pointed, prominently hyperkeratinized surface projections. **a** There is an exophytic growth pattern with most rete ridges having a pointed or square deep aspect. **b, c** However, sectioning at multiple levels revealed there was also an endophytic growth pattern relative to the adjacent normal epithelium, with deeply probing rete ridges. **d** Furthermore, there is dyskeratosis at the deepest aspect of the elongated, widened, rounded rete ridge which probes into striated muscle. The final diagnosis in this case was ‘severely dysplastic verrucous hyperplasia with evidence of early invasive squamous cell carcinoma’.

**Figure 7** ‘Blunt’ verrucous hyperplasia with prominent exophytic growth and papillary, rounded, broader processes which are less keratinized than those in **Figure 6**. The lesion arose at the junction of the lateral border of the tongue and floor of the mouth.
in situ’ in a situation where the pathologist is concerned a diagnosis of verrucous carcinoma might lead to over-treatment, but of course this risks understating the tumour’s destructive potential. There might nevertheless be occasions where such terminology is useful. The dilemma of the ‘bottom line’ diagnosis was addressed by Arendorf and Aldred, who expressed concern that a diagnosis of verrucous hyperplasia might lead to inadequate treatment. They regarded verrucous hyperplasias as verrucous carcinomas until proved otherwise, and suggested ‘ verrucous dysplasia’, ‘ verrucous carcinoma in situ’ and ‘pre-invasive verrucous carcinoma’ as alternative terms to verrucous hyperplasia. The diagnosis can reasonably remain that of verrucous hyperplasia or carcinoma where all the criteria are met and there is in addition evidence of very early conventional invasion, as long as a comment is made to this effect (see Figure 6d).

Complete excision with a 5 mm margin is the treatment of choice for both verrucous hyperplasia and verrucous carcinoma, but may be difficult as verrucous lesions can be extensive and multifocal. If it is impractical for the entire lesion to be submitted for microscopy, biopsy sampling must be thorough enough to enable conventional frank invasive malignancy to be excluded.

Papillary carcinoma

Based upon the above definitions and criteria, ‘papillary carcinoma’ is arguably a redundant term in the context of tumours of the oral mucosa, since most have a verrucous element that would enable classification of the lesion as a verrucous hyperplasia with blunt surface projections of the sort described by Shear and Pindborg (see Figure 7). The argument as to the most effective diagnostic label in terms of conveying the correct message to the surgeon also pertains to papillary dysplasias and carcinomas. Purely exophytic variants such as those shown in Figure 7 are designated papillary dysplasia, papillary squamous cell carcinoma in situ or non-invasive papillary carcinoma by some, particularly if the neoplasm is located in the larynx. Other authors have designated these lesions as verrucous hyperplasia and even verrucous carcinoma.

The epithelium lining the papillae is cytologically (as well as morphologically) dysplastic, often severely so, further suggesting this entity has more in common with verrucous hyperplasia than verrucous carcinoma. Authoritative texts disagree as to whether the surface may be keratinized or not (see Further Reading). Endophytic lesions might justifiably be designated papillary carcinoma, the presence of marked keratinocyte dysplasia technically excluding a diagnosis of verrucous carcinoma. As with verrucous carcinoma, the question becomes academic if there is more than a minimal conventionally invasive element; squamous cell carcinoma is the correct diagnosis and there is no clinical significance in adding the ‘papillary’ descriptor regardless of the surface morphology.

Proliferative (verrucous) leucoplasia

In 1985 Hansen and co-workers first reported a condition whereby an ordered sequence of events, starting with a relatively innocuous hyperkeratosis, culminated in a profoundly differentiated squamous cell carcinoma. The natural history progressed from the initial lesion, proceeding through verrucous hyperplasia, verrucous carcinoma, ‘papillary squamous cell carcinoma’ (an apparently well differentiated, conventionally invasive squamous cell carcinoma with a papillary surface) to more anaplastic squamous cell carcinoma with metastasis. Several intra-oral sites were typically involved. The diagnosis of proliferative verrucous leucoplasia could only be made retrospectively, often many years after the initial biopsy of the benign-looking hyperkeratosis. In practice, the order of events is highly variable and there is recognition that in some cases a verrucous morphology (clinically or histologically) may not necessarily develop. It is as well to warn the clinician, therefore, that a patient developing a verrucous lesion, or indeed ‘flatter’ dysplasia at more than one oral site, may possibly be at some point in the natural history of proliferative verrucous leucoplasia, and that close and prolonged follow-up is essential.

Carcinoma cuniculatum

The WHO defines carcinoma cuniculatum as ‘an exophytic, warty, slowly growing variant of squamous cell carcinoma with pushing margins. It typically involves older males’. This category of tumour is rare and the gingiva and underlying bone, more commonly of the mandible, are the usual oral sites of involvement. The tumour may have an exophytic surface, but it forms burrowing, blind-ending, often cystic downgrowths of well differentiated squamous epithelium (Figure 8). However, there may again be areas of more discohesive tumour, which may be only moderately differentiated, and it is essential those managing the patient are made aware of this. Thus, if in doubt, a sign out diagnosis of conventional squamous cell carcinoma is advisable.

Summary and conclusions

Whilst benign, reactive verrucous and papillary oral lesions usually present relatively little diagnostic difficulty, this is not the case with their dysplastic counterparts unless the lesion is at either end of the spectrum of verrucous hyperplasia and verrucous carcinoma. ‘Verrucous hyperplasia’ effectively incorporates the vast majority of lesions designated papillary dysplasia or carcinoma, and there is an argument for avoiding the latter terms for oral lesions. ‘Oral florid papillomatosis’ is synonymous with
Verrucous carcinoma and is a term which can safely be discarded and consigned to history. A verrucous hyperplasia lacking the criteria of ‘classical’ verrucous carcinoma, but nevertheless demonstrating endophytic growth, can reasonably be signed out as a verrucous carcinoma.

**Conflict of interest statement**

There are no known conflicts of interest.

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**REFERENCES**


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**Practice points**

- Ensure the biopsy is adequate. Unless the border of a verrucous lesion with the adjacent normal mucosa is present, to enable comparison between the depth of the normal and abnormal rete ridges, it may be impossible to discriminate between verrucous hyperplasia, verrucous carcinoma or, in some cases, a florid squamous papilloma.
- Verrucous hyperplasia and verrucous carcinoma are probably degrees of the same pathological process.
- An endophytic growth pattern is a *sine qua non* for the diagnosis of verrucous carcinoma.
- A purely exophytic verrucous hyperkeratoses (which is not a papilloma or one of the reactive group of lesions) should be diagnosed as a verrucous hyperplasia.
- Regardless of the degree of cytological atypia, the abnormality of the architecture indicates that a verrucous hyperplasia is at least moderate to severely dysplastic.
- An endophytic lesion, involving deep structures, with morphological features technically more in keeping with verrucous hyperplasia may nevertheless be diagnosed as verrucous carcinoma.
- Anything more than focal, early invasive disruption of the basement membrane rules out a diagnosis of verrucous hyperplasia or verrucous carcinoma; where there is typical stromal invasion by discohesive islands of malignant epithelium, the correct diagnosis is conventional squamous cell carcinoma.
- Close cooperation with the surgeon is important in the management of dysplastic and malignant verrucous lesions; the message to be conveyed is that complete excision is required with a 5 mm margin, as with a conventionally invasive squamous cell carcinoma, but that a neck dissection is unnecessary unless there are other indications.
- Bear in mind the possibility that the patient has proliferative (verrucous) leukoplakia, particularly where there are multiple lesions, or several sites are affected, over a prolonged period of time.

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**FURTHER READING**
