



Lichenoid Characteristics in Premalignant Verrucous Lesions and Verrucous Carcinoma of the Oral Cavity

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Abstract

Verrucous hyperkeratosis (VH), verrucous carcinoma (VC) and the relentless, truly pre-malignant variant proliferative verrucous leukoplakia often exhibit lichenoid histologic features that may create a diagnostic dilemma for pathologists. This study aims to evaluate and categorize the frequency and the histopathologic patterns of lichenoid features seen in these lesions. Following IRB approval, cases of VH and VC from 1994 to 2014 were retrieved from the archives of UF Oral Pathology Biopsy Service. A panel of 4 board-certified oral and maxillofacial pathologists reviewed and scored the presence or absence of 5 lichenoid features: band-like infiltrate (BLI), saw tooth rete ridges (STRR), interface stomatitis (IS), civatte bodies (CB), and basement membrane degeneration (BMD). Cases not fulfilling the stringent selection criteria were excluded. A total of 70 cases of VH and 56 cases of VC were included. Approximately 25% of both VH and VC cases exhibited 3 or more lichenoid features. By Chi square testing, BLI ($p=0.000$), IS ($p=0.005$), and CB ($p=0.026$) were significantly more common in VC than VH. Gingival lesions had significantly less frequent BLI ($p=0.004$) and IS ($p=0.024$) versus other sites. However, STRR was significantly more common in VH than VC ($p=0.000$) in the gingiva. ($p=0.002$). Statistical analysis revealed that the only significant valid association was the increased presence of band-like infiltrate in VC over VH ($p=0.001$). Lichenoid features are common in both VH and VC and may represent a nonspecific inflammatory response to the dysplasia or malignancy rather than concomitant lichenoid disease. This could lead to significant under diagnoses of these premalignant or potentially malignant lesions by pathologists.

Keywords Oral lichenoid mucositis · Verrucous hyperkeratosis · Verrucous carcinoma · Lichenoid features · Histology

Introduction

Literature on the presence of lichenoid histologic features in oral premalignant and malignant lesions is sparse. This study is a continuation of a previous project which analyzed the frequency of lichenoid features present in cases of dysplasia and squamous cell carcinoma (SCC) of the oral cavity [1]. Fitzpatrick et al. noted a preponderance of lichenoid features in these premalignant and carcinomatous lesions, particularly a band-like lymphocytic infiltrate and interface stomatitis (IS) [1]. However, the previous study did not examine premalignant verrucous lesions including verrucous hyperkeratosis (VH) and verrucous carcinoma (VC).

Both VH and VC can arise de novo or represent a histopathologic stage in the spectrum of proliferative verrucous leukoplakia (PVL) [2–4]. In addition, in many cases both VC and PVL elicit a superficial band-like lymphocytic inflammatory response [5, 6]. Importantly, lesions associated with PVL often also have a lichenoid clinical appearance potentially leading to misdiagnosis and lack of proper treatment [7].

The purpose of this study is to determine the frequency and histopathologic pattern of lichenoid features seen in VH and VC.

Materials and Methods

With institutional review board (IRB) approval, a retrospective search of the archives of UF Oral Pathology Biopsy Service between dates of January 1, 1994 to July 1, 2014 was undertaken for oral cavity lesions diagnosed as “verrucous

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carcinoma”, “verrucous-papillary hyperkeratosis”, “verrucous hyperplasia”, and “verrucous hyperkeratosis”. The original biopsy slides were retrieved and reviewed for the inclusion criteria.

Diagnostic criteria for VC was considered following recent World Health Organization descriptions: (i) “deceptively benign” morphology presenting as well-differentiated squamous epithelium forming thick and club-shaped rete pegs that push into the underlying connective tissue stroma, (ii) surface epithelium exhibiting marked keratinization in a church-spire-like fashion, (iii) thickened spinous layer is thickened lacking cytologic atypia. (iv) rare mitoses confined to the basal cell layer, and (v) lymphoplasmacytic inflammatory cell infiltrate located subjacent to the epithelium [8]. Diagnostic criteria for VH was considered as follows: (i) epithelial hyperplasia with verrucous keratotic surface, (ii) no invasion of the hyperplastic epithelium into underlying connective tissue as compared with adjacent normal oral mucosal epithelium, and (iii) verrucous hyperplastic process is superficial to the adjacent normal epithelium [9, 10]. Cases with insufficient tissue for interpretation (fragmented biopsies, biopsies lacking connective tissue, poorly oriented tissue, or excessively small biopsies), those diagnosed as benign alveolar keratosis, and cases with potential confounding factors such as extensive fungal colonization and/or large ulceration were excluded. If more than one biopsy was found for the same patient in the same location, only the earliest biopsy was included to minimize a post-biopsy healing-related influence and to avoid counting the same lesion more than once. Hybrid tumors, such as VC containing foci of conventional SCC [8] were not included in this study.

A panel of four board-certified oral and maxillofacial pathologists (DC, IB, MI, SF) reviewed all cases and scored the presence or absence of five lichenoid features: band-like infiltrate of lymphocytes in the superficial lamina propria (BLI), saw tooth rete ridges (STRR), IS, civatte bodies (CB), and basement membrane degeneration (BMD). If the characteristic was noted only focally, this was recorded as an absence of the feature.

The data was analyzed for patterns of lichenoid features related to clinical subcategories of age, gender, location and histologic diagnosis. For the purposes of this study, statistical significance was set at $p=0.05$, and both Chi square and logistic regression testing was utilized. Statistical calculations were performed using IBM SPSS Statistics (version 23; IBM).

Results

Demographics of Study Groups

126 total cases were evaluated: 70 cases of VH and 56 cases of VC. The mean age of patients with VH was 62.3 years old

(range 23–92) and for VC was 67.8 years old (range 31–88). Equal gender predilection was noted for VH cases, while slight female predilection was observed for VC. (Fig. 1).

Out of 126 total cases, the gingiva was involved in 57 (45%) and 69 involved other oral locations (55%). Cases of VH occurred more frequently on the gingiva (60%, $n=42/70$). In contrast to VH cases, VC occurred on the gingiva in only 27% ($n=15/56$) as seen in Fig. 2.

Assessment of Lichenoid Features

Examples of lichenoid features found in VH are seen in Fig. 3 and for VC in Fig. 4. Of the total cases evaluated, 24% ($n=17/70$) of VH cases demonstrated at least three lichenoid features as did 27% of VC cases ($n=15/56$) as seen in Fig. 5.

In terms of individual features, the frequency of lichenoid features noted in both VH and VC are presented in Fig. 6. For VH, BMD ($n=24/70$, 34%) was most frequently noted followed by BLI ($n=23/70$, 33%), STRR ($n=16/70$, 23%), IS ($n=11/70$, 16%), and CB ($n=11/70$, 16%). In contrast for VC cases BLI ($n=39/56$, 70%) was overwhelmingly the most commonly present feature followed by IS ($n=21/56$, 37.5%) and BMD ($n=17/56$, 30%). CB formation ($n=2/56$, 3.6%) was rarely found in VC, and STRR were not found in any cases of VC.

Statistical Analysis

When each variable was considered separately using Chi square analysis (Table 1), there was no variable predictive of three or more lichenoid features being present. However, VC cases had significantly more band-like infiltrate, IS, and CB. Specimens from the gingiva had significantly less band-like infiltrate and IS than those from other locations.

When all the independent variables were considered together via logistic regression (Table 2) the only significant association that remained was that BLI was significantly more common in VC than VH.

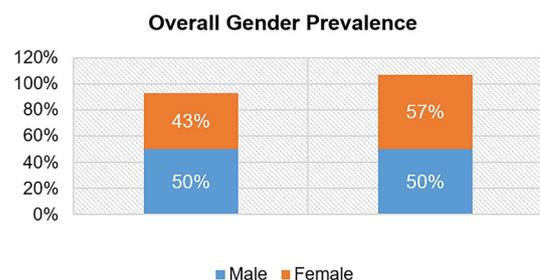


Fig. 1 Overall gender prevalence of verrucous hyperkeratosis and verrucous carcinoma cases

Fig. 2 Location of verrucous hyperkeratosis and verrucous carcinoma cases

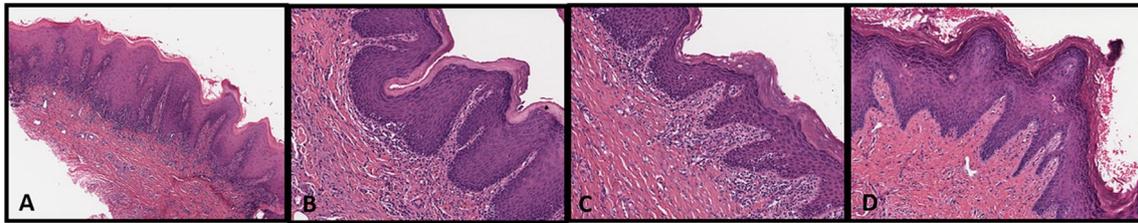
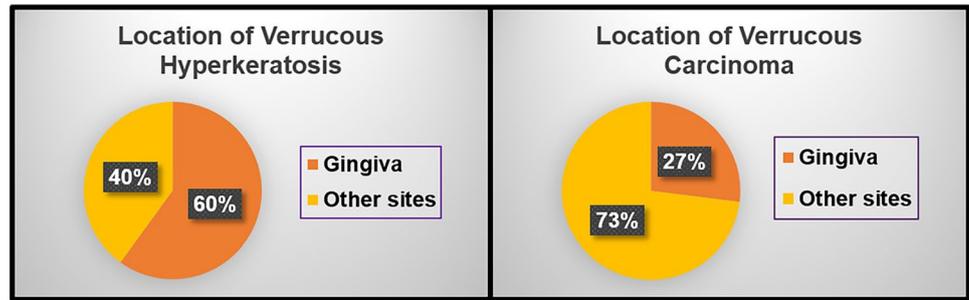


Fig. 3 Lichenoid features in verrucous hyperkeratosis cases. **a** Band-like inflammatory infiltrate (H&E, ×4), **b** basement membrane degeneration (H&E, ×10), **c** interface stomatitis (H&E, ×10), **d** saw-tooth rete ridge formation and Civatte body formation (H&E, ×5)

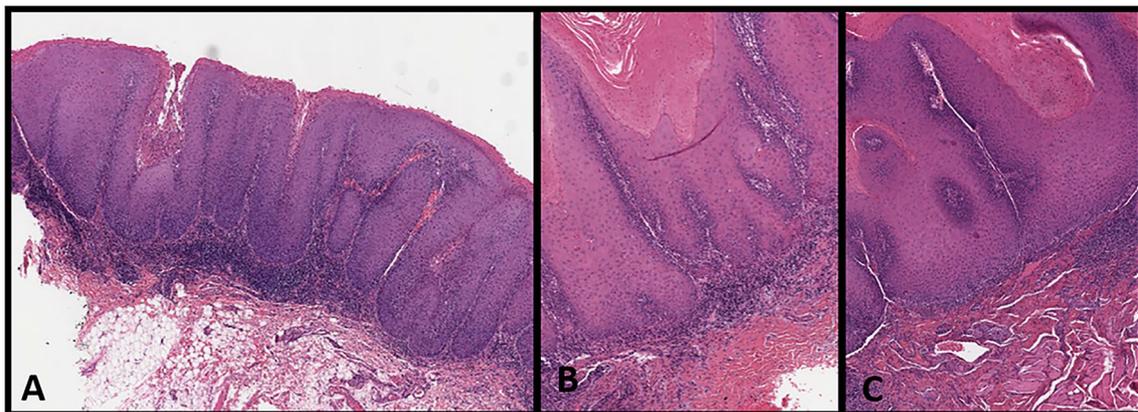


Fig. 4 Lichenoid features in verrucous carcinoma cases. **a** Band-like inflammatory infiltrate (H&E, ×2), **b** basement membrane degeneration (H&E, ×5), **c** interface stomatitis (H&E, ×4)

Discussion

Oral lichen planus (OLP) is a well-recognized and relatively common mucocutaneous disorder resulting from an abnormal T-lymphocyte immune response targeting the basal layer of epithelial cells presenting with characteristic clinical and histologic features. However, these features are not always specific for OLP and may be seen as an inflammatory response to a host of other factors including local irritants such as rough dental restorations, medications, and even epithelial dysplasia and malignancy [7, 11, 12]. The histologic term “lichenoid” is also used for any lesion exhibiting a superficial BLI (mainly lymphocytic)

infiltrate in the stroma. However, these same changes are seen in a variety of other conditions including lupus erythematosus, erythema multiforme, graft-versus-host disease, and even T-cell lymphomas [7, 13]. Therefore, BLI is often a nonspecific and unreliable feature [1, 13].

Historically, a combination of microscopic features such as BLI, STRR, CB, BMD, and IS were considered for a diagnosis of OLP [12]. However, recently proposed modification of diagnostic criteria for OLP now emphasizes the histologic features of BLI, BMD, and IS, omitting STRR and CB as diagnostic features and strictly excluding cases exhibiting dysplasia or verrucous surface change (Table 3) [12].

VH and VC are both often associated with the PVL spectrum of lesions, where a significant diagnostic

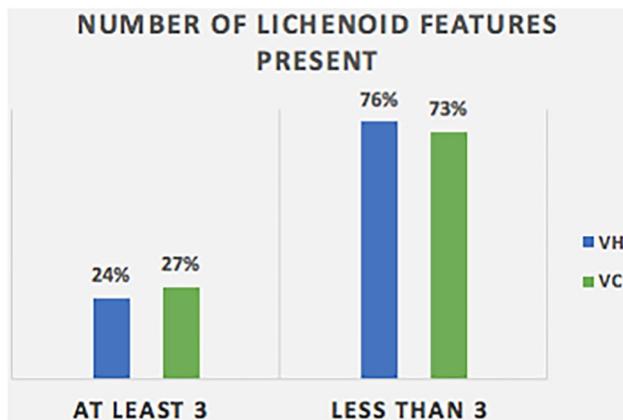


Fig. 5 Overall lichenoid features present in verrucous hyperkeratosis and verrucous carcinoma cases

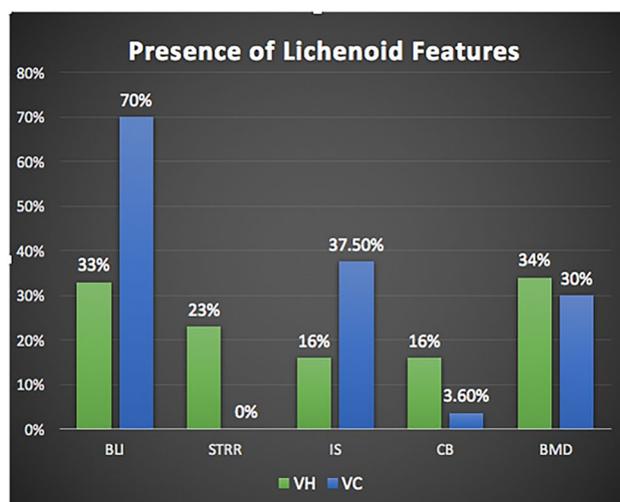


Fig. 6 Specific lichenoid features in verrucous hyperkeratosis and verrucous carcinoma cases

challenge may occur due to clinical and histologic overlap with benign conditions including OLP and benign keratosis. This condition is significant to clinicians and pathologists both due to the difficulty in diagnosis and the high rate of malignant transformation which likely exceeds 50% in most estimates [14]. The inflammatory response within PVL type lesions has been described as often showing an interface mucositis with a lymphocyte rich inflammatory response in the superficial lamina propria [11]. PVL, VH and VC all occur frequently in an older population. OLP shows similar age preponderance. Moreover, the oral sites affected by PVL, VH and VC are similar to those noted in patients with OLP. The demographics and location distribution of lesions of PVL, VH and VC patient groups in our study generally coincided with those noted in literature [9, 10, 13, 15–21].

Approximately one quarter of both VH and VC cases in our study had three or more lichenoid features present (24% and 27% respectively). This was slightly lower than the previous related study demonstrating three or more lichenoid features in 29% of overall dysplasia and SCC cases (39% of low-grade dysplasia cases, 16% of high-grade dysplasia, and 34% of SCC cases) [1]. The pattern of these findings highlights the apparent lack of a strictly linear association between increased level of lichenoid response to increased severity of dysplastic or malignant change, which is unexpected. In addition, given the longstanding association of PVL demonstrating lichenoid appearance both clinically and histologically with VH and VC, it was unexpected that the number of lichenoid features measured in VH and VC was lower than that of the low-grade dysplasia cases measured in the prior study [1, 7]. While BLI was the most frequently observed lichenoid feature found in this study it was found in slightly more cases of VC than VH. BLI was also the most common lichenoid feature noted in the previous study of oral dysplasia and SCC [1].

In the current study, when each variable (age, gender, location, and diagnosis) was analyzed separately, but no single variable that was predictive of whether three or more lichenoid features would be present. However, VC cases had significantly more BLI, IS, and CB. Gingiva had significantly less BLI and IS than other locations. STRR was rare in VH and not observed in VC since broad pushing bulbous rete ridge formation is a characteristic of this entity.

When all the independent variables were considered together, the only significant association was that BLI was more common in VC than VH. Therefore, this particular feature may increase with increased invasiveness of the overlying lesion. All other significant associations from the Chi square analysis were lost on logistic regression, which indicates the inconclusiveness of any demographic or clinical feature in predicting a lichenoid response to premalignant or malignant lesions in the oral cavity.

The limitations of this study are mainly due to the subjective nature of the assessment of lichenoid changes by the reviewers. In the prior study, samples were assessed separately by panelists and agreement statistics revealed difficulty with consensus agreement in the analysis of lichenoid features [1]. In the current study, group consensus between panelists was utilized rather than independent evaluation, though both methods may potentially introduce bias and inconsistency to the assessment of lichenoid appearing features within the samples. This is an inherent problem when attempting to standardize diagnostic features and criteria among pathologists.

The results of this study investigating the frequency of lichenoid features in VH and VC along with the prior study demonstrating the same findings in oral dysplasia and SCC provide add support to the newly proposed AAOMP OLP

Table 1 Association of lichenoid features to clinical features and diagnosis of study cases: Chi square testing, two sided

Lichenoid feature	Age group (<40, 40–59, 60+)	Gender (M, F)	Diagnosis (VH vs VC)	Location (gingiva vs all other sites)
Overall presence of three or more lichenoid features	$p=0.346$	$p=0.995$	$p=0.749$	$p=0.544$
BLI	$p=0.485$	$p=0.486$	$p=0.000$ 23/70 (33%) of VH 39/56 (70%) of VC	$p=0.004$ 20/57 (35%)—gingiva 42/69 (61%)—other sites
STRR	$p=0.040$ 0/5 (0%)—<40 y.o. 9/37 (24%)—40–59 y.o. 7/82 (8.5%)—60+y.o.	$p=0.179$	$p=0.000$ 16/70 (23%) of VH 0/56 (0%) of VC	$p=0.002$ 13/59 (22%)—gingiva 3/69 (0.4%)—other sites
IS	$p=0.402$	$p=0.416$	$p=0.005$ 11/70 (16%) of VH 21/56 (37.5%) of VC	$p=0.024$ 9/57 (16%)—gingiva 23/69 (33%)—other sites
CB	$p=0.608$	$p=0.592$	$p=0.026$ 11/70 (16%) of VH 2/56 (3.5%) of VC	$p=0.212$
BMD	$p=0.895$	$p=0.492$	$p=0.640$	$p=0.082$

Bold values indicate statistically significant

Significance $p < 0.05$, 95% confidence interval

VH verrucous hyperkeratosis, VC verrucous carcinoma, M male, F female, BLI band-like lymphocytic infiltrate, STRR sawtooth rete ridge formation, IS interface stomatitis, CB civatte body formation, BMD basement membrane degeneration

Table 2 Association of lichenoid features to clinical features and diagnosis of study cases: binary logistic regression

Lichenoid feature	Age group (<40, 40–59, 60+)	Gender (M, F)	Diagnosis (VH vs VC)	Location (gingiva vs all other sites)
Three or more lichenoid features present	$p=0.783$	$p=0.950$	$p=0.891$	$p=0.602$
BLI	$p=0.686$	$p=0.515$	$p=0.001$	$p=0.133$
STRR	$p=0.679$	$p=0.282$	$p=0.997$	$p=0.078$
IS	$p=0.605$	$p=0.480$	$p=0.072$	$p=0.146$
CB	$p=0.615$	$p=0.659$	$p=0.058$	$p=0.649$
BMD	$p=0.906$	$p=0.643$	$p=0.290$	$p=0.072$

Bold value indicate statistically significant

Significance $p < 0.05$, 95% confidence interval

VH verrucous hyperkeratosis, VC verrucous carcinoma, M male, F female, BLI band-like lymphocytic infiltrate, STRR sawtooth rete ridge formation, IS interface stomatitis, CB civatte body formation, BMD basement membrane degeneration

diagnostic criteria guidelines which call to strictly exclude cases with dysplasia or verrucous surface change from a diagnosis of OLP [1, 12].

Further sub-classification of the lymphocytic infiltrate in VH and VC utilizing immunohistochemical analysis and comparing to OLP may aid in better understanding of the inflammatory response and the role it plays in the progression from VH to VC and later on to SCC.

Conclusions

Lichenoid features are commonly seen in both VH, VC and PVL and is often misleading to pathologists. In these cases, the lichenoid features likely represent a nonspecific lymphocytic response to the invasion of the connective tissue, dysplasia or malignancy rather than a distinct

Table 3 2016 AAOMP Proposed Criteria for Diagnosis of OLP (Reprinted in part with permission from: Cheng et al. [12])

Clinical criteria	<p>Multifocal symmetric distribution</p> <p>White and red lesions exhibiting one or more of the following forms:</p> <ul style="list-style-type: none"> – Reticular/papular – Atrophic (erythematous) – Erosive (ulcerative) – Plaque – Bullous <p>Lesions are not localized exclusively to the sites of smokeless tobacco placement</p> <p>Lesions are not localized exclusively adjacent to and in contact with dental restorations</p> <p>Lesion onset does not correlate with the start of a medication</p> <p>Lesion onset does not correlate with the use of cinnamon-containing products</p>
Histopathologic criteria	<p>Band-like or patchy, predominately lymphocytic infiltrate in the lamina propria confined to the epithelium lamina propria interface</p> <p>Basal cell liquefactive (hydropic) degeneration</p> <p>Lymphocytic exocytosis</p> <p>Absence of epithelial dysplasia</p> <p>Absence of verrucous epithelial architectural change</p>

lichenoid disease. Pathologists should be cognizant of the possibility of the presence of lichenoid features in VH, VC and PVL in order to avoid misinterpretation and potentially under-calling VH, VC or PVL with lichenoid features.

Compliance with Ethical Standards

Conflict of interest All authors declare no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Waiver of informed consent was obtained from the institutional review board of University of Florida College of Dentistry (IRB#201300744).

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