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Clinicopathologic analysis of verrucous hyperplasia, verrucous carcinoma and squamous cell carcinoma as part of the clinicopathologic spectrum of oral proliferative verrucous leukoplakia: A literature review and analysis

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A B S T R A C T

Objective: Proliferative verrucous leukoplakia is classified as a potentially malignant disorder because of its high rate of malignant transformation. PVL progresses in a series of clinical stages where the early stage represents multiple, multifocal leukoplakias with a high recurrence rate. The intermediate and late stages are clinically exophytic lesion, diagnosed microscopically as verrucous hyperplasia that often progresses into verrucous carcinoma and/or squamous cell carcinoma. There is no single histologic definition and the diagnosis is retrospective following observed progression of the disorder. The goal of the current study was to conduct a literature review and analysis of PVL in the later stages to gain further knowledge on their clinicopathologic features.

Data sources: Medline's PubMed and Google Scholar were searched for adequately documented cases from 1985 to 2018. References of published articles were searched for additional cases.

Review methods: Overall, 57 manuscripts were analyzed. 35/57 manuscripts provided adequate data on the clinicopathologic features in the premalignant and malignant stages.

Results: Malignant transformation rate was 50% (average of 57 months). Gingiva, palate and buccal mucosa were the most common locations. Clinicopathologic features included; well differentiated carcinoma (78%), perineural invasion (3%), lymph node metastasis (4%); distant metastasis (0%), average duration of illness (65 months), DOD-dead of disease (44%). Moderate dysplasia, severe dysplasia and carcinoma in situ were exceptionally uncommon in the premalignant stages (0.8%).

Conclusion: Prognostic factors such as perineural invasion, lymph node metastasis and distant metastasis were uncommon occurrences which may have practical implications on treatment. Further studies are needed to substantiate our findings.

1. Introduction

Proliferative verrucous leukoplakia (PVL), a unique type of oral leukoplakia, was first recognized as a distinct clinicopathologic entity in 1985 by Hansen L, et al [1]. The current World Health Organization (WHO) includes PVL under the category of "oral potentially malignant disorders" due to its high rate of malignant transformation and high rate of recurrence over a time span of many years in multifocal locations throughout the oral cavity [2]. PVL progresses in a somewhat predictable series of clinicopathologic stages. In 1985, Hansen et al. proposed a criteria system that consisted of 5 stages (graded 1–10) that represented the microscopic/clinical spectrum of appearance [1]. The PVL stages range from benign, innocuous lesions to exophytic premalignant and malignant tumors. There are no specific histologic criteria for PVL, and the diagnosis is retrospective, dependent on the ability to recognize its progressive, recurrent clinicopathologic stages [2]. Early stage lesions appear clinically as either homogenous or non-homogenous leukoplakias and are diagnosed microscopically as either hyperkeratosis or hyperkeratosis with lichenoid features. The early stage lesions are indistinguishable from the more common unifocal leukoplakias which often causes a delay in diagnosis where it becomes more difficult to manage therapeutically. The intermediate stage represents the premalignant stage and present clinically as verrucous lesions that are diagnosed microscopically as verrucous leukoplakia or verrucous hyperplasia (VH), terms that are used interchangeably. The late stage represents the malignant stage which appears as an exophytic mass with a verrucous surface contour, are clinically larger and more extensive than VH and are diagnosed microscopically as verrucous carcinoma (VC). Over time, new and recurrent tumors often appear in the final stage, an invasive squamous cell carcinoma (PVL-SCCA) [1].

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Since 1985, numerous case reports and case studies have been reported in the literature which has contributed greatly in our knowledge of the demographic characteristics of patients with PVL. There is general agreement that PVL is more common among elderly women who do not engage in high risk habits like smoking [3–7]. The most common location for PVL development is controversial yet most previous studies have reported the gingiva, palate and buccal mucosa to be the most common location with a minority of cases that present on the tongue and lip [8,9]. Silverman and Gorsky [5] noted a higher prevalence of premalignant lesions on the tongue although in the malignant stage, the gingiva was the commonest location. Several studies have explored potential treatment options for PVL although most have demonstrated only limited success in arresting the appearance of recurrent lesions or its progression to late stage invasive carcinoma.

The few treatment studies that have reported notable beneficial effects on their patient cohort include a study by Schoelch et al. [10] where a combined treatment with CO_2 and ND:YAG laser resulted in only a 57% recurrent rate, Femiano et al. [11] who treated his patients with a combination of surgery and methisoprinol (Isoprinosine; a synthetic compound with reported antiviral and immunomodulating properties) which resulted in only a 16% relapse and an additional 2 studies where photodynamic therapy seemed helpful in managing PVL patients [12,13]. An early study conducted by Silverman and Gorsky, found that treatment with Vitamin A analogues or antioxidant nutrients failed to show any beneficial effects in their patient cohort [5].

The clinicopathologic features of PVL in the premalignant and malignant stages has garnered much less attention in the literature and much remains unknown. In addition, PVL etiopathogenesis remains elusive. The goal of the current study was to conduct a retrospective literature review and analysis on the available clinicopathologic data of PVL in the premalignant and malignant stages published in the literature from 1985 to 2018 and a discussion of the available studies on the diagnostic criteria and potential etiopathogenesis in order to gain a better understanding of PVL.

2. Materials and methods

2.1. Data collection methods

The English language literature was searched for adequately documented PVL cases and original research that were published between 1985 and 2019. Medline's PubMed and Google Scholar were searched using the keywords PVL, proliferative verrucous leukoplakia, PVL associated squamous cell carcinoma (PVL-SCCA), verrucous carcinoma and verrucous hyperplasia. References of published articles were searched for additional cases. Studies, yet not review articles, on potential etiopathogenesis and diagnostic criteria were searched and summarized. Review articles were analyzed for additional information on the premalignant and malignant PVL stages.

2.2. Inclusion and exclusion criteria (Table 1 and Figs. 1–5)

The inclusion criteria were eligible case studies of PVL that documented sufficient data on all the stages of PVL (hyperkeratosis, hyperkeratosis with lichenoid features, verrucous hyperplasia, verrucous carcinoma and/or PVL associated squamous cell carcinoma (PVL-SCCA) and that fulfilled the diagnostic criteria proposed by either Hansen et al. [1], Batsakis et al. [14], Cerero-Lapiedra et al. [15] or Carrard et al. [16]. The exclusion criteria included reported cases that did not fulfill the diagnostic criteria or where the patient presented with a solitary lesion. In addition, in order to reduce bias, authors who published more than one publication using a repeated cohort of patients were analyzed separately. In these studies, the patient cohort from the most recent publication was compared with prior reports and summarized accordingly.

2.3. General data [4,5,8–12,17–48]

There were 84 documented case reports/case series on PVL in all stages of development of which 57 manuscripts (n = 383 lesions) provided adequate information and were included in the study. The study was conducted in 2 parts: Part 1: all 57 manuscripts were analyzed for information that contributed to: a) average time from initial diagnosis to malignant transformation, b) microscopic presence of dysplasia in either the early stage (hyperkeratosis/hyperkeratosis with lichenoid features) or verrucous hyperplasia. Case studies that did not specify the level of dysplasia were categorized as non-specific and excluded from the analysis. Part 2: Of the total 57 case studies, 35 studies provided adequate clinicopathologic information on the premalignant (VH) and malignant stages (VC or PVL-SCCA). The total patient cohort (VH, VC and PVL-SCCA) was 297 that presented with a total of 405 premalignant and malignant tumors. Each case was segregated into a group depending on its progressive stage: A) premalignant stage- verrucous hyperplasia (VH) (n = 23 tumors) which is defined as lesions with a verrucous or papillary surface contour and microscopically, they both present with verrucous processes lined by well-differentiated, squamous epithelium, either sharp or heavily keratinized or blunt with a thick parakeratin layer [49]. B) early malignant stage -verrucous carcinoma (VC) (n = 48 tumors) and C) late malignant stage-invasive squamous cell carcinoma (PVL-SCCA) (n = 334 tumors). Information on patient demographics (age, gender, location) and lifestyle (smoking habits) was recorded for each patient. Location was categorized into one of 3 groups: a) gingiva, palate and buccal mucosa, b) tongue/floor of mouth, c) labial mucosa. The clinicopathologic data extracted and analyzed included: a) prognostic microscopic features (tumor grade, perineural invasion, depth of invasion), b) metastatic rate (lymph node metastasis and distant metastasis), c) duration of illness (DOI), d) dead of disease (DOD), e) treatment. Microscopic depth of invasion was categorized as superficially invasive (< 0.4 cm or as stated by the author) or deeply invasive (> 0. 4 cm). Duration of illness was defined as the time from initial diagnosis of PVL-SCCA and death from the disease.

3. RESULTS (Tables 2 and 3)

3.1. Microscopic evidence of dysplasia

Overall, there was documentation of dysplasia for 261 PV L lesions and tumors (patients n = 102) although 82/261 (31%) lesions/tumors did not document the specific level/grade of dysplasia and were excluded from the analysis. The 179 lesions and tumors (patients n = 70) thus included for analysis showed: A) early stage PVL (leukoplakia/lichenoid lesions) (n = 154): a) no dysplasia/mild dysplasia (n = 129/154; 84%) b) moderate dysplasia (n = 20/154; 13%) c) severe dysplasia or carcinoma in situ (n = 5/154; 3%), B) VH/VC (n = 25): a) no dysplasia/mild dysplasia (n = 24/25; 96%) b) moderate dysplasia (n = 1/25; 4%) c) severe dysplasia or carcinoma in situ (n = 0). Total cohort: a) no dysplasia/mild dysplasia (n = 153/179; 85%), b) moderate dysplasia (n = 21/179; 12%), c) severe dysplasia/carcinoma in situ (n = 5/179; 3%). No cases of severe dysplasia or carcinoma in situ in VH or VC were reported. The average time span from initial diagnosis to malignant transformation was 57 months.

4. Premalignant/malignant tumors (VH, VC and PVL-SCCA) [4,5,9,11,16,17,19,21,23,24,27,28,31,32,35,50–54]

4.1. Epidemiology

Age and gender were known in all cases and presented more commonly in females (n = 206; 69.4% with a male to female ratio of 1.0: 2.3) and the average age was 62.34 years (median: 64 years). Information on smoking was known for 220 patients of which 154 (70%) were non-smokers and 66 (30%) were smokers. Location was

Table 1
Proposed and suggested diagnostic criteria for PVL.

AUTHOR/YEAR	CLINICAL/MICROSCOPIC SPECTRUM	NOTES
Hansen et al. (1985)	1) Normal (grade 0) 2) Leukoplakia (grade 2) 3) Verrucous leukoplakia (grade 4) 4) Verrucous carcinoma (grade 6) 5) Papillary SCCA (grade 8) 6) Less differentiated SCCA (grade 10)	Clinicopathologic stages 1-10
Batsakis et al. (1999)	1) Leukoplakia 2) Non-homogenous leukoplakia with dysplasia 3) Verrucous hyperplasia 4) Verrucous carcinoma 5) Squamous cell carcinoma	Modified version of Hansen et al.
Cerero-Lapiedra et al. (2010)	**MAJOR** 1) > 2 leukoplakias 2) Verrucous lesions 3) Lesions have spread 4) Recurrence in previously treated area 5) Microscopically, a lesion in any PVL stage **MINOR** 1) A single leukoplakia or the summary of multiple leukoplakias that are ≥ 3 cm in size 2) Female patients 3) Non-smokers 4) Disease evolution of > 5 years	Diagnosis requires 3 major criteria or 2 major and 2 minor criteria (including the microscopic findings)
Carrard et al. (2013)	1) Leukoplakia with verrucous areas involving > 2 oral subsites 2) The total size of the lesions in all involved sites ≥3 cm 3) Distinct evolution of at least 5 years characterized by spreading or ecurrence in previously treated area 4) The availability of at least one biopsy to rule out VC or SCCA	

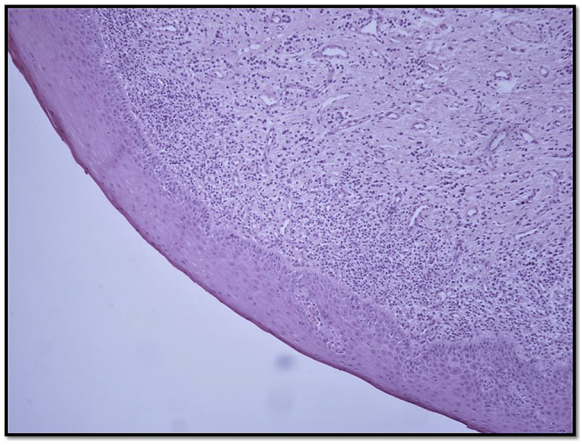

Fig. 1. Microscopic example of an early stage PVL lesion showing hyperkeratosis with lichenoid features and an intense subjacent band-like lymphocytic reaction (HE stain ×40).

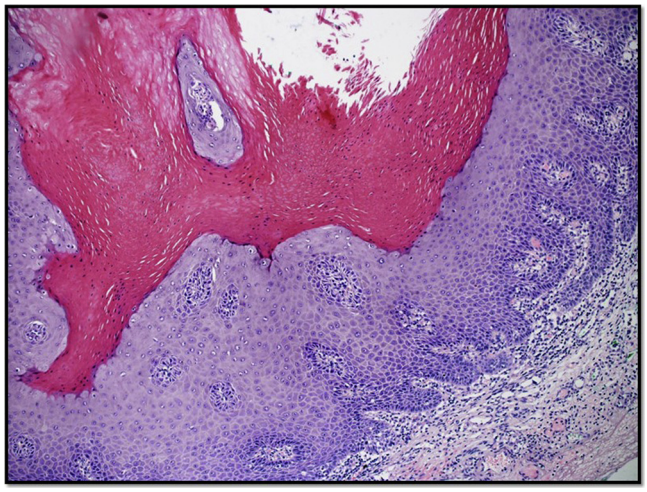

Fig. 2. Microscopic example of intermediate stage PVL-verrucous hyperplasia: note the heavily keratinized, verrucous surface contour and well differentiated squamous epithelium (HE stain ×100).

known for 66 VH/VC tumors and included: a) gingiva, palate and buccal mucosa (n = 50; 76%), b) tongue/floor mouth (n = 14; 21%), c) labial mucosa (n = 2; 3%). Location was known for 222 PV L-SCCA tumors and included: a) gingiva, palate and buccal mucosa (n = 169; 76%), b) tongue/floor mouth (n = 47; 21%), c) labial mucosa (n = 5; 3%).

4.2. Clinicopathologic features PVL-SCCA [4,5,11,16,19,21–24,41,50–53]

17 published studies provided adequate data on the late malignant stage (PVL-SCCA), often without a description of a precursor pre-malignant stage or VC.

Relevant data from each study was extracted and compiled into a table that reflected an average of the total data. The microscopic characteristics were documented in a minority of studies and included: A) tumor grade (n = 52 tumors); a) well differentiated (n = 40; 77%), b) moderately differentiated (n = 10; 19%, c) poorly differentiated (n = 2; 4%), B) perineural invasion (38 tumors); a) present (n = 1; 3%), b) absent n = 37; 97%), C) microscopic depth of invasion was known for 72 tumors and included, a) superficially invasive (n = 36; 50%), b) deeply invasive (n = 36; 50%). Only a minority of studies documented the presence or absence of metastasis and included; A) lymph node status (52 tumors); a) present (n = 2 tumors; 4%), b) absent (n = 50 tumors; 96%), B) distant metastasis (38 tumors); a) present (n = 0), b) absent (n = 38; 100%).

4.3. Treatment modalities [4,5,9,20,22,24,25,29,34,50,52,53]

Treatment modality was known for 137 patients and included surgery alone (n = 66; 46%), surgery with radiation (n = 40; 30%),

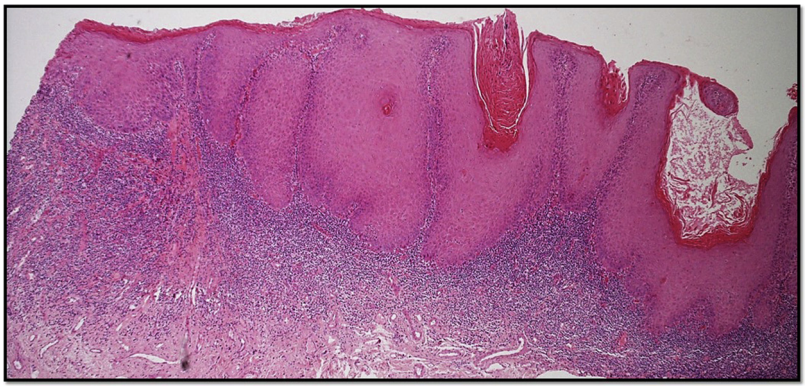

Fig. 3. Microscopic example of late stage PVL-verrucous carcinoma: hyperkeratinized, well-differentiated stratified squamous epithelium and broad rete processes extending into the connective tissue stroma (HE stain ×40).

surgery with radiation and a neck dissection (n = 12; 9%), surgery with radiation and laser treatment (n = 10; 8%), surgery with laser (n = 5; 4%), retinoids alone (n = 3; 2%) and radiation with chemotherapy and laser treatment (n = 1; 0.7%).

4.4. DOD and DOI [4,5,11,16,19,21–24,41,50,51]

DOD was known for 113 patients of which 34 (30%) died from their disease. DOI was known for 60 patients who survived an average of 65 months before succumbing to the disease.

5. Discussion

PVL is an uncommon condition that the current WHO has designated as an "oral potentially malignant disorder" [2]. It has been described by others as an aggressive variant of multifocal leukoplakia due to its higher malignant potential and recurrence rate [7]. PVL develops over a time span of many years and is difficult to control because they are resistant to most conventional therapies, the etiopathogenesis is unknown and the early stage lesions are virtually indistinguishable from the more common leukoplakia which impedes on our ability to make an early diagnosis.

Although attention has been drawn to the premalignant and malignant stages of PVL, etiology and factors influencing its natural history remains to be established.

5.1. Diagnostic criteria (Table 1)

The first diagnostic criteria system was proposed by Hansen et al. [1], where he described 5 progressive clinicopathologic stages (graded from 1 to 10) in the diagnostic spectrum of PVL. Since 1985, numerous case reports, case studies and reviews were reported in the literature which has contributed greatly to our knowledge of the demographic characteristics of PVL patients. Most agree that PVL occurs most commonly in elderly women and smoking, a high-risk factor for conventional squamous cell carcinoma, does not seem to influence PVL development [3–7,55]. Location remains debatable although most published articles have noted the gingiva, buccal mucosa and palate to be the primary site of occurrence and these features are reflected in the present review [7,8,26]. Currently, there is no globally accepted, single histologic definition for PVL but based on the accumulated data on PVL, Batsakis et al. [14], Cerero-Lapiedra et al. [15] and Carrard et al. [16] each suggested a modification of Hansen's proposed system. Cerero-Lapiedra et al. [15] suggested that female patients without a history of smoking, a progressive time span of more than five years and total size of the combined multifocal lesions should be included as a minor

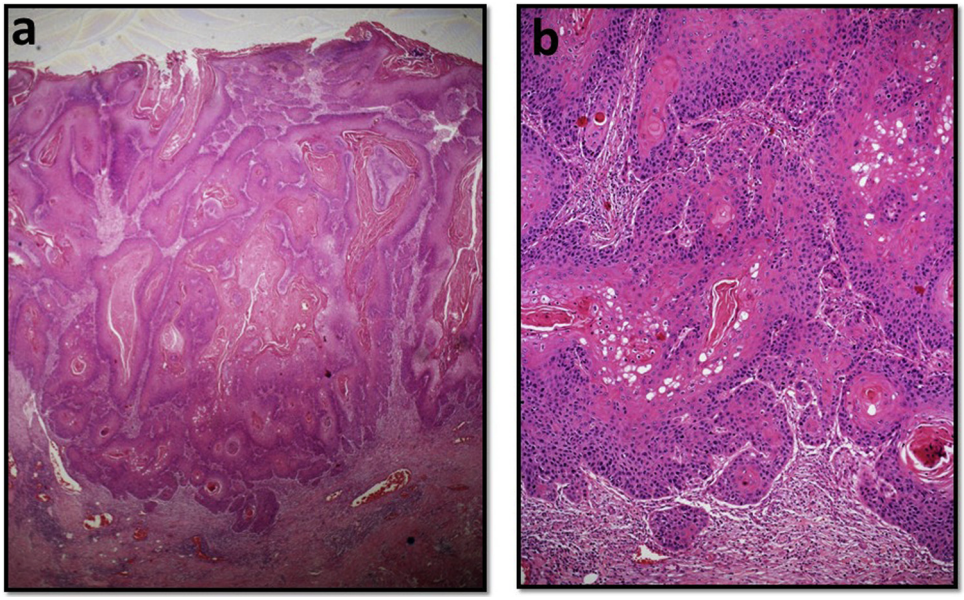

Fig. 4. Microscopic example of PVL-SCCA: A) well differentiated squamous cell carcinoma (HE stain ×40) B) nests of neoplastic cells invading into the superficial connective tissue stroma (HE stain ×100).

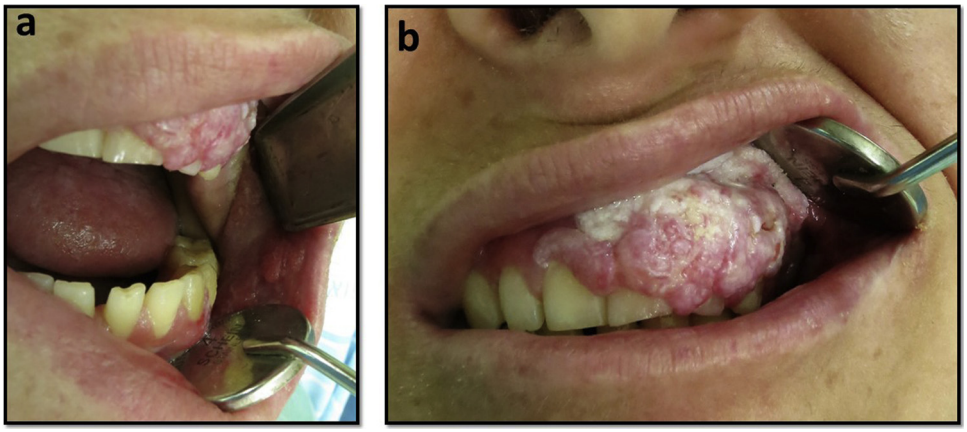

Fig. 5. Clinical presentation of late stage, multifocal PVL: A) Clinical aspect of an exophytic, wart-like lesions on the left maxillary gingiva suspicious for p-scca and an exophytic lesion on the left buccal mucosa suspicious for VH. B) Closer view of the maxillary gingival tumor.

Table 2
Epidemiologic features of PVL patients (n = 297) who presented with pre-malignant & malignant tumors (n = 405).

Epidemiology of total patient cohort (n; %)		
GENDER (n = 297)		
Female	n = 206; 69.4	
Male	n = 91; 30.6	
Age at initial presentation (n = 297)	Average: 62.34 years Median: 64 years	
Habits (n = 220/297)		
Non-smokers	n = 154; 70%	
Smokers	n = 66; 30%	
Known location (n = 288; %)	**VH and VC (n = 66)**	**PVL-SCCA (n = 222)**
1 Gingiva/buccal mucosa/palate:	50 (76)	169 (76)
2 Tongue/floor of mouth:	14 (21)	47 (21)
3 Labial mucosa:	2 (3)	5 (2)

1. Premalignant-VH lesions: (n = 2).
2. Early malignant-VC tumors: (n = 48).
3. Late malignant-PVL-SCCA tumors: (n = 334).

criterion for diagnosing PVL. In summary, the diagnosis is based on recognizing the progressive stages of PVL and while not a criterion for diagnosis, clinicopathologic correlation is essential for the benefit of early detection.

5.2. Premalignant/early malignant stages (VH/VC)

In our review of the premalignant and malignant PVL tumors, only 23 cases of VH and 48 cases of VC were defined as such or provided adequate clinicopathologic information and were available for analysis. This relatively low number likely represents an underestimation of the actual number of cases. VH, which precedes VC in the clinicopathologic spectrum of PVL, are intermediate or transitory stages that preceding PVL-SCCA. The clinical entity VH was first reported by Shear and Pindborg [35] without mention of its association with PVL. Since that time, the significance of VH in the clinicopathologic spectrum of PVL lesions has been recognized and most regard VH as potentially pre-cancerous [36]. VC is considered a low grade, slow growing and well differentiated tumor with extremely low metastatic potential and presents most commonly on the gingiva and alveolar ridge [56]. VH and VC may share overlapping histologic and clinical features and are often indistinguishable. Clinically, both are white or pink exophytic lesions with a verrucous or papillary surface contour and microscopically, they both present with verrucous processes lined by well-differentiated, squamous epithelium, either sharp or heavily keratinized or blunt with a thick parakeratin layer [49]. According to Shear and Pindborg [35], the principal distinguishing feature is that the verrucous processes in VH are superficial to the adjacent normal epithelium whereas VC presents with broad rete processes that extend considerably deeper than the adjacent normal epithelium.

Controversy exists as to whether VH is a precursor to VC [38] or a morphological variant [36]. Previous studies that support the claim that VH is a precursor of VC include Paral et al. [45] who found that a reduction in stromal α smooth muscle actin and an increase in CD34 + dendritic cells favor a diagnosis of VH, Mallik et al. [46] who conducted a ploidy analysis study and showed that all cases of oral squamous cell carcinoma (OSCCA), 86% of VC and 39% of VH were aneuploid and Klieb et al. [40] who reported that an immunohistochemical panel of increased ki-67, p53 and stromal cell expression of matrix metalloproteinase (MMP)-1, markers that indicate tumor progression, favors a diagnosis of VC. In contrast, Sharma et al. [47] compared the expression of p53 (tumor suppression gene) in VH and VC and found similar rates of expression and Lin et al. [43] found that the expression of p53, mouse double minute (MDM)-2, p21 and heat shock protein (HSP)-70 were unable to differentiate between VH and VC. These studies seem to provide evidence to support the hypothesis that VH is a morphologic variant of VC. Controversy exists regarding the presence of dysplastic changes before the development of PVL-SCCA [8,35,36,49]. In our analysis of PVL in **all** stages of development, there were 261 PV L cases that documented the microscopic presence of dysplasia although 31% did not specify the level/grade of dysplasia and were excluded from the analysis. Therefore, a total of 179 cases that were analyzed (early lesions; n = 154; VH and VC; n = 25). In total, 153/179 (86%) cases documented the presence of either no dysplasia or mild dysplasia and 26/179 (14%) cases documented the presence of moderate dysplasia. No cases of severe dysplasia or carcinoma in situ were reported. These findings agree with some [8] yet not others [35,36]. In a study by Rosnah et al. [49] she notes that, “if some of the VHs did transform into VC, then it would be difficult to explain as to how these dysplastic VHs transform into VCs which have minimal cellular atypia”. VC is a low-grade tumor that is known to present without dysplasia and with “a deceptively benign” microscopic appearance [56–58]. According to Neville et al. [58], the lesional epithelial cells *(in VC)* generally show a normal maturation pattern with no significant degree of cellular atypia”. Rosnah et al. [49] suggested that incomplete sampling of the surgical VC specimens may have missed the presence of foci of cellular atypia in VC which could better explain this phenomenon of transformation of VH (with atypia and mild dysplastic features) to VC.

Based on the results of our review, we suggest that cellular atypia found in VH may be the result of the intense, band-like lymphocytic response found at the epithelial/connective tissue interface that is present in most cases of VH [57]. The controversy remains unresolved. A consensus report published by an expert working group from South

Table 3
Literature analysis of the known clinicopathologic characteristics.

CHARACTERISTICS	no. patients with available data	no. tumors with available data	Results: n (%)
Microscopic evidence of dysplasia*			
-Early stage PVL (leukoplakia/lichenoid lesions)	n = 86	n = 154	None/mild: 129 (84) Moderate: 20 (13) Severe/in situ: 5 (3)
-Premalignant/early malignant tumors (VH/VC)	n = 16	n = 25	None/mild: 24 (96) Moderate: 1 (4) Severe/in situ: 0
Time to malignant transformation	–	n = 124/357	Average: 57 months
PVL-SCCA Tumor grade	n = 31	n = 52	Well: 40 (77%) Moderate: 10 (19%) Poor: 2 (4%)
Perineural invasion	n = 11	n = 38	Present: 1 (3%) Absent: 37 (97%)
Depth Invasion	n = 32	n = 72	Superficial: 36 (50%) Deep: 36 (50%)
Lymph node metastasis	n = 25	n = 52	Present: 2 (4%) Absent: 50 (96%)
Distant metastasis	n = 11	n = 38	0
DOI**	n = 60	n/a	Average: 65 months
DOD***	n = 113	n/a	Alive: 79 (70%) Dead: 34 (30%)
Treatment	n = 137	n/a	Surg: 66 (46) Surg/Rad: 40 (30) Surg/Neck/Rad: 12 (9) Surg/Laser/Rad: 10 (8) Surg/Laser: 5 (4) Retinoids: 3 (2) Rad/Chemo/Laser: 1 (.7)

Abbreviations: DOD, dead of disease; DOI, duration of illness; surg, surgery; rad, radiation; neck, neck dissection; chemo, chemotherapy.
* 82/261 (31%) cases were categorized as non-specific due to inadequate information.
** DOI (duration of illness) is the time from PVL-SCCA diagnosis to death.
*** Statistics on the death rate is based on the number of reported deaths.

Asia at a meeting of "Terminology and Criteria for Verruco-papillary Lesions of the Oral Cavity" ended without an anonymous consensus and made a claim that some cases of VH present with epithelial dysplasia [49]. The cases of PVL where dysplasia is absent may impede on our ability to diagnose PVL in the early-intermediate stages which may have an impact on the disease progression. Further studies are required. Predicting which PVL cases will progress to an invasive scca is a subject of several investigations. Three studies reported that ploidy analysis can predict malignant transformation [24,29,37]. Bagan et al. [48] found that increased Il-6 salivary and serum levels had potential for monitoring PVL patients for recurrences and progression. The optimal treatment method for VH remains uncertain. Successful treatments reported in the literature include topical 5-aminolevulinic acid-mediated photodynamic therapy (ALA-PDT), with or without cryotherapy [42,44] or shave excision followed by simple cryosurgery [41].

In conclusion, most agree that VC and VH represent a critical stage in PVL's progression to a malignancy. We suggest that because VH is so commonly associated with PVL, the term should be reserved for recurrent exophytic lesions, highly suspicious for being part of the clinicopathologic spectrum of PVL progression. The lack of dysplasia in most cases impedes on our ability to recognize PVL before it progresses to PVL-SCCA. An alternate method and valuable diagnostic markers for early detection is greatly needed.

5.3. Invasive PVL associated squamous cell carcinoma (PVL-SCCA)

It has been reported that 50–70% of PVL lesions undergo malignant transformation [5,25,33,55] In our analysis, a malignancy developed from 52% of all reported PVL cases but the data is inconclusive as the follow-up time was unknown in many cases. The average time for a progression to a malignancy was 57 months. In a study by Borgna et al. [55] they noted that aggressive surgical intervention in the premalignant phase of PVL may not influence the rate of malignant transformation. Our literature search revealed 17 studies that provided enough data for analysis. Like the early stage lesions, most tumors were located on either the gingiva, palate or buccal mucosa with a minority of cases on the tongue or labial mucosa. The microscopic analysis showed that 77% were well differentiated and only 4% were poorly differentiated. The depth of invasion was described as deeply invasive in 50% of cases. Perineural invasion and lymph node metastasis, significant prognostic factors, was infrequently documented. Only one case series study reported a perineural invasion rate of 4% [50]. Six studies with a total of 52 PV L-SCCA documented the lymph node status of which only 2 patients presented with a lymph node metastasis (4%) [4,41]. There were no reports of a distant metastasis. The survival rate for PVL patients is controversial. Our analysis revealed that 34/113 (30%) of the PVL patients were reported to have died from the disease. It is difficult to determine if this figure is reliable as the follow-up time in many cases was unknown. Further studies are required in order to validate this finding. In comparison to PVL-SCCA, the reported 5-year survival for conventional oral SCCA is approximately 50% [59]. The analysis revealed an average DOI (from initial diagnosis of PVL-SCCA to death) of 65 months. Many patients with PVL-SCCA experience a long history of multiple and multifocal malignant tumors followed by progressively more aggressive treatments in order to control the disease, yet their average DOI is longer than for patients with conventional oral SCCA. A study by Wang et al. [60] reported a median DOI of only 36 months for conventional oral SCCA.

In conclusion, the better microscopic and clinical prognostic factors together with the unique clinical characteristics of PVL supports the contention of others that PVL-SCCA may be a unique clinical variant of oral SCCA [15]. More studies on a larger series of cases is warranted in order to validate these findings.

5.4. Etiopathogenesis

Several studies addressed the issue of etiopathogenesis [3,5,6,18,29,33,43,50,60–65]. Silverman and Gorsky [5], pioneers in the study of PVL, claimed that there is no evidence of immunologic disease or any associated immunodeficiency in patients with PVL. “Field cancerization”, a concept first proposed by Slaughter et al. [61] has been suggested as a causative factor in PVL development. Field cancerization states that the development of multifocal tumors within the oral cavity may be a result of chronic exposure of the oral mucosa to carcinogens such as tobacco or other unrelated genetic factors which puts the entire upper aerodigestive tract at risk. Hypothetically, “field cancerization” may be a contributing factor in PVL pathogenesis except that most PVL patients are non-smokers, a known carcinogen for oral cancer. A virus was also investigated as a causative agent for PVL development as the tumors are multifocal, recurrent and clinically exophytic. An association of high-risk human papilloma virus (HPV) was found by some [62] yet most others have disputed this finding [6,18,43,50,54,63]. A study by Bagan et al. [64] concluded that Epstein-Barr virus (EBV) did not participate in PVL etiopathogenesis and Garcia-lopez et al. [65] ruled out herpes virus and polyomavirus as the causative agent. Silverman and Gorsky et al. [5] reported that the presence of candida was commonly detected in PVL but denied that candida was linked to its recurrences or malignant transformation. Several genetic studies are reported in the literature. Kresty et al. [33] discovered that homozygous deletion, loss of heterozygosity and mutation in cell cycle related genes p16INK4a and p14ARF were frequent findings in many PVL cases and Gouvea et al. [29] discovered high levels of Mcm2 expression in PVL. One study investigated the use of transforming growth factor (TGF) - alpha expression to distinguish between PVL-SCCA and conventional OSCCA but the results were inconclusive [66]. Akrish et al. [3] reported that as opposed to conventional OSCCA, tumor associated fibroblasts (CAFs) were an infrequent finding in the PVL-SCCA microenvironment. Previous studies have shown that the presence of CAFs in the microenvironment of conventional oral scca is associated with poor prognostic factors and decreased survival [67].

5.5. Perspectives

Since 1985 when PVL was first discovered, numerous case reports and studies have been published which has contributed greatly to our understanding of this entity, yet much remains unknown. The absence of dysplasia in the early lesions and premalignant tumors may impede on our ability to diagnose PVL early which may have an impact on the disease progression. The data from this study seems to show that the gingiva, buccal mucosa and palate are the most common locations for PVL-SCCA development and prognostic factors such as perineural invasion, lymph node metastasis and distant metastasis are infrequent findings which may have practical implications on therapy. Several challenges should be addressed and include, a) a better understanding of PVL etiopathogenesis b) the discovery of an established method for early detection. Further studies are needed in order to substantiate our findings.

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Declaration of Competing Interest

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