Review Article

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An Insight into Proliferative Verrucous Leukoplakia

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ABSTRACT

Proliferative verrucous leukoplakia (PVL) is a progressive multifocal lesion of the oral mucosa with no discernible aetiology. It is a rare form of oral leukoplakia illustrating resistance to all therapy with subsequent high malignant transformation rate along with frequent recurrences. The PVL is a progressive condition, witnessed commonly in aged women, over 60 years at the time of diagnosis. It initially develops as a white plaque of hyperkeratosis which eventually becomes a multifocal disease with confluent, exophytic, and proliferative features showing different grades of dysplasia. Use of tobacco does not seem to have a substantial influence on the incidence and progression of PVL. The prognosis is poor for this apparently innocent looking white lesion with malignant transformation rate of 43-100%. Literature was reviewed through search engines like Google Scholar and PubMed to find relevant studies using the keyword "Proliferative Verrucous Leukoplakia" published between 1985 to 2020. Original research, reviews, case reports, case series were included in the study. This review highlights the requirement of the simplified universal criteria, which will help in early diagnosis to improve the therapeutic approach. More clinical trials with prolonged follow-up controls are necessary to evaluate an effective therapeutic approach for the treatment of PVL.

Keywords: Exophytic; hyperkeratosis; proliferative verrucous leukoplakia.

INTRODUCTION

Proliferative verrucous leukoplakia (PVL) was first described by Hansen in 1985 as a long-term progressive condition, which develops primarily as a white plaque of hyperkeratosis that ultimately becomes a multifocal disease.[1] The PVL has more destructive biological behaviour than other forms of leukoplakia characterised by an inclination toward multifocality; a high rate of recurrence; and a higher malignant transformation rate.[2] The initial stages of this entity cannot be distinguished grossly or microscopically from conventional localised and multifocal conventional leukoplakia.[3] It is important to note that PVL is a clinical diagnosis for leukoplakias that comprehend a spectrum of clinical and histopathological stages. It is prone to exhibit recurrence and may manifest as malignancy clinically and histopathologically.[4]

The diagnosis of the lesion relies on the progressive clinicopathologic follow-up of the patient. Four broad phases characterised this entity: (1) focal early presentation; (2) geographic expansion with time; (3) development of a verrucous/warty appearance; and (4) development of cancer.[3]

METHODOLOGY

Literature was reviewed through search engines Google Scholar and PubMed to find relevant studies using the keyword "Proliferative Verrucous Leukoplakia" published between 1985 to 2020.

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Original research, reviews, case reports, case series were included in the study.

RESULTS AND DISCUSSION

Aetiology

The aetiology of PVL is idiopathic. The role of tobacco in the occurrence and progression of the lesions is uncertain as PVL seems to occur in both in smokers and non-smokers.[5-7] Bagan et al. traced few PVL patients with smoking habits which eventually developed into oral squamous cell carcinoma (OSCC) over a period of time.[8] These studies indicate that tobacco has little or no role in the aetiology of PVL.

Some authors have also reported Human Papilloma Virus (HPV) as a probable cause for PVL.[9,10] Palefsky et al. studied nine lesions from seven patients with PVL and found that eight (89%) lesions were positive for HPV and out of which, seven were positive for HPV16.[2,11] Campisi et al. reported HPV DNA in 24% of PVL cases and 25.5 % of oral leukoplakia. They concluded no significant difference in HPV positivity between PVL and oral leukoplakia groups.[6] In contrast with the above finding, Bagan et al. reported undetectable HPV in the 10 frozen biopsy tissue of PVL patients.[12] This coincides with the findings of Fettig et al.[13] The PVL has also been reported in association with Epstein Barr virus (EBV) and Candida infection. Bagan et al. 2013 found 66.6% cases of PVL positive for Epstein Barr Virus (EBV).[14] Silverman et al. stained 38 PVL cases using bromocresol green (BCG) agar medium, Periodic Acid Schiff stain, and speciation germ tube testing. Out of which 19 were positive for candida albicans.[9]

Clinical features

PVL is seen as more common in elderly females.[9,15] The average age at the time of diagnosis is above 60 years (Table 1).[7,15] It occurs primarily as a white plaque of hyperkeratosis. Then progresses to develop a multifocal lesion with exophytic and proliferation with different grades of dysplasia.[16,17] The PVL can also initially present as oral lichen planus or lichenoid reaction both clinically and histopathologically.[5,18] Two extensive studies on PVL indicated buccal mucosa to be the most common site with occurrences of 57.4% and 76.6%.[9,10] Similarly, the lip was the least commonly involved site with the occurrence of 13.3% and 16.6%. Reichart and Philipsen in 2003 concluded buccal mucosa, gingiva, and alveolar ridges to be the most commonly affected site.[19] Contradicting with these findings Bagan et al. indicated gingiva (89%) as the most common site followed by buccal mucosa (47.2%), and lips (7.2%.) of the total cases (Table 1).[8]

Histopathological features

Hansen et al. proposed histological stages of PVL in the spectrum as **Grade 0:** Normal mucosa **Grade 2:** Hyperkeratosis (clinical leukoplakia) **Grade 4:** Verrucous hyperplasia **Grade 6:** Verrucous carcinoma **Grade 8:** Papillary squamous cell carcinoma (SCC) **Grade 10:** Less well-differentiated squamous cell carcinoma. The PVL can have naive appearing hyperkeratosis to noticeable less differentiated squamous cell carcinoma.[3] It is mandatory to reflect on overall clinical presentation along with histopathological examination to conclude it to be PVL. The progressive histological features may include features that may overlap with lichen planus or be allied with areas that are or have been diagnosed as lichen planus.[5] PVL can also be misdiagnosed as lichen planus due to the presence of interface lymphocytic infiltrate within the superficial lamina propria like lichen planus. The intense lymphocytic infiltrate present may obscure the visualisation of the basement membrane. Apoptotic cells and eosinophilic ovoid (Civatte, colloid, cytoid, hyaline) bodies may also present. With time, there may be conforming histopathological findings of accentuated keratosis with a progressive corrugated or verruciform surface.[4,5] The overall histopathologic features may have a variety of presentations; localised flat hyperplasia and hyperkeratosis, multifocal hyperkeratotic lesions with or without dysplasia, verrucous hyperplasia, and verrucous and/or conventional squamous carcinoma.[3]

Diagnostic criteria

Hansen et al. first described 10 grades range of

Table 1: Published data of proliferative verrucous leukoplakia.

Study	Total cases	Gender		Age	Site		Habit	Treatment		Follow-up year	Malignant transformation		Recurrence (%)
		Male	Female			Cases (percent)	Cases (percent)		Cases (percent)			Cases (percent)	
Hansen et al. (1985)	30	6	24	27-90 (Average 66 years)	Buccal mucosa Hard and soft palate Alveolar mucosa Tongue Floor of mouth Gingiva Lip	23 (76.6) 18 (60) 16 (53.3) 15 (50) 8 (26.6) 5 (16.6) 4 (13.3)	18 (62)	Radiation Surgery Chemotherapy Multiple excision Laser surgery Retinoids Other None	18 (60) 17 (56.6) 6 (20) 5 (16.6) 4 (13.3) 2 (6.6) 2 (6.6) 2 (6.6)	(1-20) average 6.1years	VC PSCC SCC	9 (30) 12 (40) 5 (16.6)	90
Zakrzewska et al. (1996)	10	5	5	42-81 (Average 63.5 years)	Buccal mucosa Hard and soft palate Alveolar mucosa and gingiva Tongue Fauces Lip	8 (80) 3 (30) 8 (80) 6 (60) 2 (20) 2 (20)	7 (70)	Radiation Surgery Chemotherapy Laser photodynamic	1 (10) 6 (60) 1 (10) 5 (50) 4 (40)	(5-15 years) average 7.5 years	VC PSCC SCC	4 (40) 2 (20) 4 (40)	90
Silverman and Gorskey (1997)	54	11	43	22-89 (Average 62 years)	Buccal mucosa Palate Tongue Floor of mouth Gingiva Lip	31 (57.4) 19 (35.1) 29 (53.7) 22 (40.7) 29 (53.7) 9 (16.6)	17 (31)	Surgery Surgery and radiation	41 (75.9) 11 (20.3)	1-39 (average 11.6 years)	SCC	38 (70)	85
Ghazail et al.	9	2	7	24-76 (Average62 years)	Multifocal single site Tongue Other single site	6 (66.7) 2 (22.2) 1 (11.1)	6 (67)	Surgery Laser and surgery None	7 (78) 1 (12) 0 (0)	(2-8 years) 4.7 years	Multifocal carcinoma	4 (45)	55.6
Fettig et al. (2000)	10	6	4	51-82 years (Average 65 years)	Gingiva Gingiva and floor of mouth	9 (90) 1 (10)	3 (37.5) Data not available for 2	Excision Stripping Laser Maxillectomy Resection	8 (42.1) 1 (5.26) 5 (26.3) 2 (10.5) 3 (15.7)	1-6 years	VC PSCC SCC	2 (20) 1 (10) 3 (30)	100

Study	Total cases	Gender		Age	Site		Habit	Treatment		Follow-up year	Malignant transformation		Recurrence (%)
		Male	Female			Cases (percent)	Cases (percent)		Cases (percent)			Cases (percent)	
Bagan et al. (2003)	30	6	24	70.97±12.73 years	Upper gingiva Lower gingiva Hard palate Soft palate Right buccal mucosa Left buccal mucosa Dorsum of tongue Ventral aspect of tongue Upper lip Lower lip	23 (76.7) 26 (86.7) 15 (50) 4 (13.3) 17 (56.7) 17 (56.7) 12 (40) 13 (43.3) 7 (23.3) 8 (26.7)	7 (23.3)	Surgery Laser CO2 treatment	24 (80) 18 (60)	1-10 years (Average 4.7 years)	VC SCC	8 (27) 19 (63)	86.7
Campisi (2004)	58	22	36	54-79 (Average 66.6 years)	Not reported		17 (29.3)	Not Report			VC SCC	3 (5.1) 22 (37.5)	Not reported
Klanerit et al. (2006)	6	1	5	65.8±10 years	Alveolar ridge/gingiva Buccal mucosa Palate Tongue Buccal sulcus	6 (100) 3 (50) 3 (50) 2 (33.3) 2 (33.3)	1 (16.6)	Surgery Laser	5 (83.3) 1 (16.6)	12-25 Years	SCC VC Multiple primary carcinoma	3 (30) 1 (16.6) 3 (30)	Not reported
Morton et al. (2007)	3	1	2	73-89 years	Gingiva Gingiva and buccal mucosa Hard palate	1 (33.3) 1 (33.3) 1 (33.3)	2 (66.6)	Surgical excision Resection of maxilla	2 (66.6) 1 (33.3)	0.2 to 7.5 years	VC SCC	1 (33.3) 2 (66.6)	66.6
Gondolfo (2009)	47	10	37	40-86 (Average 65.9 years)	Alveolar crest Buccal mucosa' Gingiva Floor of mouth Lip	41 (87.2) 33 (70.2) 22 (46.8) 8 (17) 6 (12.7)	17 (36.8)	NOT REPORTED		6.89 years	VC SCC	9 (19.1) 32 (68)	NOT REPORTED

Study	Total cases	Gender		Age	Site		Habit	Treatment		Follow-up year	Malignant transformation		Recurrence (%)
		Male	Female			Cases (percent)	Cases (percent)		Cases (percent)			Cases (percent)	
Bagan et al. (2011)	55	36	19	61.69±11.76 years	Gingiva Buccal mucosa Tongue Lips Palate	49 (89.0) 26 (47.2) 27 (49) 4 (7.2) 15 (27.2)	20 (36.3)	Surgery Laser CO_2	21 (38.1) 34 (61.8)	7.53±4.18 years	SCC	27 (49)	85
Pola Garcia (2016)	14	11	3	35-69 years (Average 56.4 years)	Hard palate Right buccal mucosa Left buccal mucosa Tongue Soft palate Gingiva Maxillary alveolar mucosa Mandibular alveolar mucosa Vestibular mucosa	7 (50) 13 (92.8) 13 (92.8) 3 (21.4) 1 (7.1) 5 (35.7) 3 (21.4) 1 (7.1) 2 (14.2)	3 (21.4)	Surgery Laser Topical corticosteroid Systemic retinoid Systemic steroid	4 (28.5) 7 (50) 14 (100) 2 (14.2) 1 (7.1)	6.3 -24.3 years (Average 14.5)	SCC VC	3 (21.4) 1 (7.1)	NOT REPORTED

PVL (normal, clinical leukoplakia, verrucous hyperplasia, verrucous carcinoma, papillary squamous cell carcinoma, and less differentiated squamous carcinoma with intermediates), so the disease may have any of these histologic stages, as well as intermediates and combinations during its progressive clinical course.[10] Several studies have followed this grading system. Batsakie et al.[17] have reduced the number of histologic stages to four with intermediates: clinical leukoplakia without dysplasia, verrucous hyperplasia, verrucous carcinoma, and conventional squamous cell carcinoma.

Diagnostic criteria given by Ghazail et al.[20] is based upon clinical description by Hansen et al.[10] and histopathological scoring of Batsaki et al.:[17]

1. The lesion starts as homogenous leukoplakia without evidence of dysplasia at the first visit.
2. With time, some areas of leukoplakia become verrucous.
3. The disease progresses to the development of multiple isolated or confluent lesions at the same or different sites.
4. With time, the disease progresses through the different histopathological stages reported by Hansen et al.
5. The appearance of new lesions after treatment.
6. A follow-up period of no less than one year.[20]

Gandolfo et al.[21] has also given criteria based upon criteria given by Hansen et al.[10] and Batsaki et al.[17] which is as follows:

An initially innocuous lesion characterised by a homogenous plaque that progresses over time to an exophytic, diffuse, usually multifocal, lesion with a verrucous epithelial growth pattern.

Histopathologically, PVL changes gradually from a simple plaque of hyperkeratosis without dysplasia to verrucous hyperplasia, verrucous carcinoma, or OSCC.[21]

Cerero Lapiedra et al.[1] have proposed major and minor criteria for the diagnosis of PVL

Major criteria:

A. A leukoplakia lesion with more than two different oral sites, which is most frequently found in the gingiva, alveolar processes, and palate.

B. The existence of a verrucous area.

C. That the lesions have spread or engrossed during the development of the disease.

D. That there has been a recurrence in a previously treated area.

E. Histopathologically, there can be from simple epithelial hyperkeratosis to verrucous hyperplasia, verrucous carcinoma, or oral squamous cell carcinoma, whether in situ or infiltrating.[1]

Minor criteria:

a. An oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas.

b. That the patient be female.

c. That the patient (male or female) be a non-smoker.

d. A disease evolution higher than five years.

To make the diagnosis of PVL, it was suggested that one of the two following combinations of the criteria mentioned before were met.

1. Three major criteria (being E among them) or
2. Two major criteria (being E among them) + two minor criteria.[1]

Carrard et al.[22] suggested simplifying the diagnostic criteria of PVL by omitting the distinction between major and minor criteria proposed by Cerero Lapiedra et al.[1] Accordingly, they modified diagnostic criteria as follows:

- Leukoplakia showing the presence of verrucous or wart like areas, involving more than two oral subsites
- When adding all involved sites, the minimum

size should be at least 3 cm

- A well-documented period of disease evolution of at least five years, being characterised by spreading and enlarging and occurrence of one or more recurrences in a previously treated area
- The availability of at least one biopsy to rule out the presence of verrucous carcinoma or squamous cell carcinoma.[22]

Treatment

The treatment of PVL lesions is quite challenging with an overall poor prognosis. Multidisciplinary treatment approaches such as surgery, radiation, chemotherapy, retinoid, topical steroid, photodynamic therapy cryotherapy, and chemotherapy are done.[5,23,24] There is no consistently applicable treatment protocol reported so far, and many of the lesions tend to rebound after treatment.[25]

Molecular studies

In a study done by Gopalkrishnan et al., HPV 16 was identified in two cases of PVL along with positive p53 protein accumulation without p53 mutation.[26] In a study of DNA ploidy analysis of PVL, five out of six patients had aneuploidy development before the diagnosis of carcinoma.[15] The mean cytoplasmic optical density for TGF alpha expression was significantly higher in PVL and OSCC than in normal mucosa. The mean optical density of PVL was slightly higher than that of OSCC however this difference was not significant.[27] In a study of comparison of expression of P53, ki-67, and p16 in SCC associated with PVL to conventional SCC there were significant differences in p53 but not ki-67 or p16 expression.[28,29]

A study of levels of IL-6 among OSCC, PVL, and healthy controls, there were significant differences in serum and saliva IL-6 levels among the three groups. OSCC patients had the highest serum and saliva IL-6 levels followed by PVL and control group.[30]

Malignant transformation

Malignant transformation rates of PVL vary between 43% to 100% among different studies.[6,7,9,10] PVL has demonstrated malignant transformation into squamous cell carcinoma, papillary squamous cell carcinoma, verrucous carcinoma, carcinoma cuniculatum.[13,15] Of the 55 cases studied by Bagan et al., at least one squamous cell carcinoma developed during the follow up in 27 patients with a malignant transformation rate of 49.1%. According to Gondolfo et al. patients with PVL develop verrucous carcinoma more commonly compared to SCC. He also concluded that the patients with PVL on the lateral border of the tongue showed a lower malignant transformation compared to the masticatory mucosa with a higher tendency for the same. The PVL is reported to have a more common transformation into squamous cell carcinoma.[6,7]

SUMMARY

PVL has a high inclination for dysplasia and malignant transformation mainly because it displays resistance to many therapeutic attempts. The most thought-provoking aspect of PVL is early diagnosis and management. This review highlights the development of the simplified universal criteria, which will aid in easy early diagnosis to establish as inevitable lesion to improve the therapeutic approach. More clinical trials with prolonged follow-up controls are necessary to evaluate an effective therapeutic approach for the treatment of PVL.

Conflict of interest: None.

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