ORAL DISEASES

Oral Diseases (2010) 16, 328–332. doi:10.1111/j.1601-0825.2009.01632.x

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REVIEW ARTICLE

Proliferative verrucous leukoplakia: a concise update

J Bagan[1], C Scully[2], Y Jimenez[3], M Martorell[1]

[1]*Valencia University and Hospital General Universitario de Valencia, Valencia, Spain;* [2]*University College London, London, UK;* [3]*Valencia University, Valencia, Spain*

Proliferative verrucous leukoplakia (PVL) is of uncertain etiology but may be associated with human papillomavirus (HPV) infection. Proliferative verrucous leukoplakia is seen mainly in older women, beginning as a simple slow-growing, persistent leukoplakia that tends to spread and become multifocal and affect the gingival frequently. In time, PVL develops exophytic, wart-like or erythroplakic areas that become squamous carcinomas. Proliferative verrucous leukoplakia appears to resist to all attempts at therapy and often recurs.

Oral Diseases (2010) **16**, 328–332

Keywords: proliferative verrucous leukoplakia; oral

Introduction

Proliferative verrucous leukoplakia (PVL) is a rare condition first described by Hansen *et al*, 1985 who presented 30 patients with this particular form of oral leukoplakia. Proliferative verrucous leukoplakia begins as a simple slow-growing, persistent hyperkeratosis that tends to spread and become multifocal and, in time develops exophytic, wart-like, or erythroplakic areas that become carcinomas. PVL appears to resist to all attempts at therapy and often recurs.

The World Health Organization (WHO) also described the PVL with a high rate of malignant transformation (Barnes *et al*, 2005). Cabay *et al*, 2007 defined *PVL* as a distinct clinical form of oral leukoplakia which in turn is defined by its progressive clinical course, changing clinical and histopathologic features, and potential to develop into cancer.

The term that has been used before until the description of Hansen *et al*, 1985 was oral florid papillomatosis. (van der Waal and Reichart, 2008).

A search of the PubMed English literature revealed only 49 articles in which the term Proliferative verrucous leukoplakia appeared in the title or abstract (Table 1). Many of the articles are case reports of one or very few cases (Torres-Pereira *et al,* 2008; Shopper *et al*, 2004; Reichart and Philipsen, 2003; Vigliante *et al*, 2003; Sciubba, 2001; Baughman and Boland, 2001; Greer *et al*, 1999; Haley *et al*, 1999; Eversole, 1997). It is not surprising therefore that there is little definitive knowledge on the causes of the disease or the best management. We summarize here the little that is known from this literature search.

Correspondence: Prof. Jose V. Bagan, MD, DDS, PhD, Hospital General Universitario, Servicio de Estomatología, Avda/Tres Cruces s/n, 46014 Valencia, Spain. Tel: 34 961972127, Fax: 34 961972127, E-mail: bagan@uv.es
Received 11 May 2009; revised 01 September 2009; accepted 08 September 2009

Demography

Proliferative verrucous leukoplakia is more common in elderly women who have had lesions of leukoplakia for many years (Hansen *et al*, 1985). Silverman and Gorsky, 1997 studied 54 patients, and the mean age of their group was 62 years with a ratio of women/men of 4 to 1. Most other authors reported similar patterns, and we presented 30 cases (Bagan *et al*, 2003) with a mean age 70.9 ± 12.73 years, and 80% were women.

Clinical characteristics

Proliferative verrucous leukoplakia commences as one or more homogeneous leukoplakic areas and, over time, the lesions enlarge and affect other locations, especially the gingivae. The buccal mucosa, gingiva, and alveolar ridges were most often affected in the report by Reichart and Philipsen, 2003. Others have found lesions more frequently on the gingiva and tongue (Silverman and Gorsky, 1997). In our series, 87% had lesions on the gingiva (Bagan *et al*, 2003) (Figures 1–5).

Gandolfo *et al*, 2009 studied forty-seven patients with PVL. Lesions were most frequently observed on the alveolar crest (87.2%), with gingival involvement in 46.8% cases.

Etiopathogenesis

Viral studies

Proliferative verrucous leukoplakia is of uncertain etiology. An association with human papillomavirus (HPV) infection has been suggested (Eversole, 2000) and Palefsky *et al* (1995) studying nine lesions from seven

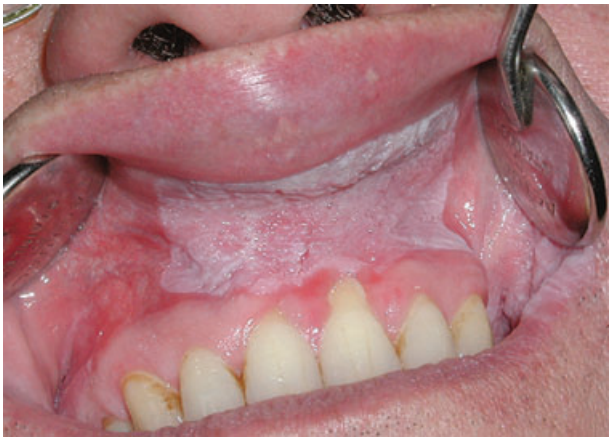

Figure 1 Proliferative verrucous leukoplakia on the upper gingiva and vestibular sulcus

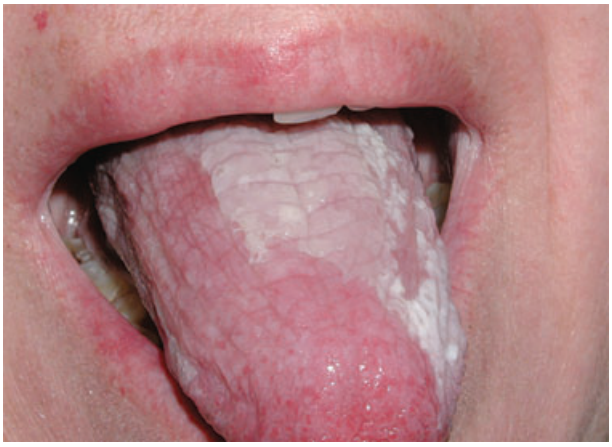

Figure 2 Proliferative verrucous leukoplakia on the dorsum of the tongue

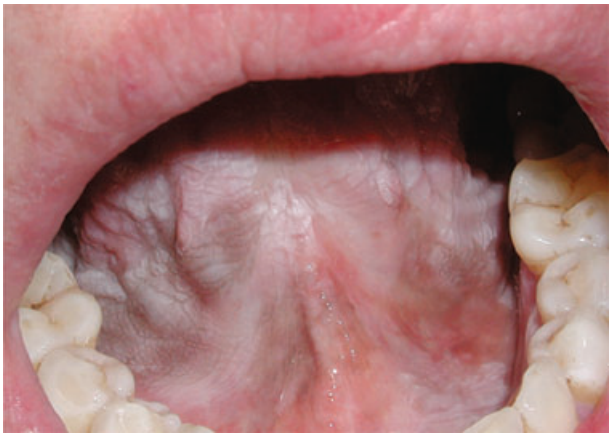

Figure 3 Proliferative verrucous leukoplakia on the flower of the mouth

patients with PVL found out that eight (89%) were positive for HPV and seven contained HPV-16. They suggested, therefore, that HPV-16 infection may play an

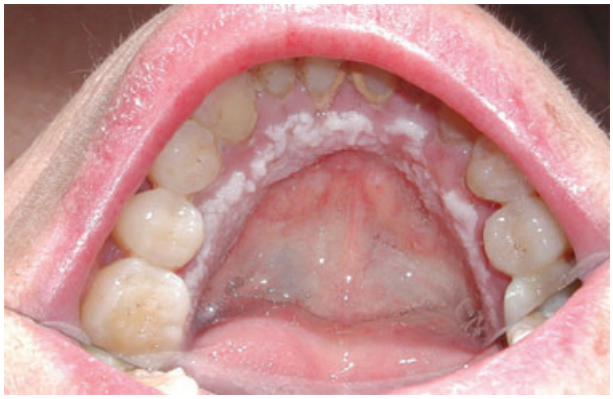

Figure 4 Proliferative verrucous leukoplakia on the lower gingiva

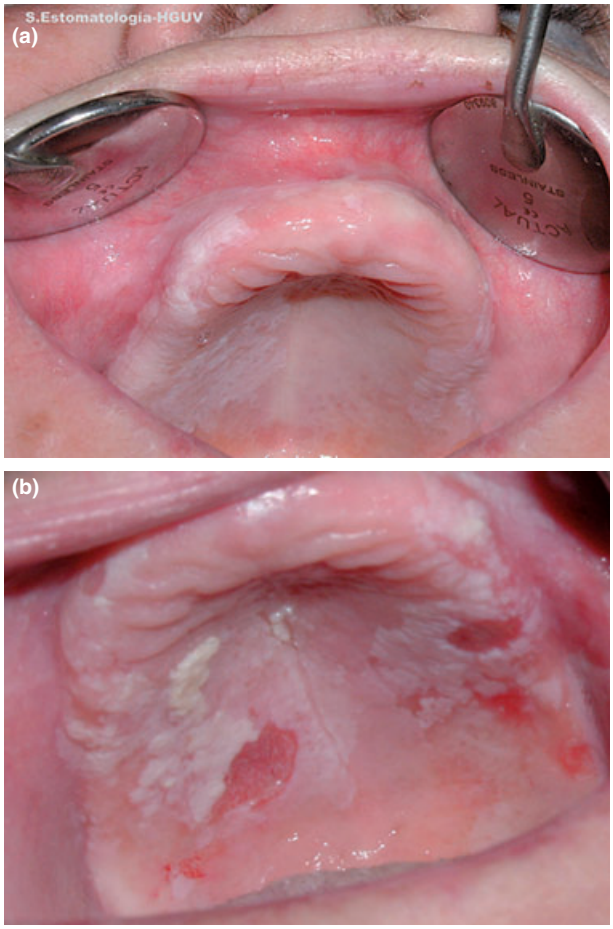

Figure 5 (**a**) Proliferative verrucous leukoplakia (PVL) on the palate and (**b**) three years later the patient developed an oral squamous cell carcinoma in the same location

important role in these lesions. Gopalakrishnan *et al* (1997) studied mucosal samples from 10 PVL patients, 10 oral squamous cell carcinomas (OSCC), and 10 controls of normal mucosa, and found HPV-16 and 18 in two of eight p53 positive cases of PVL, and HPV-16 in two out of seven p53 positive OSCC, and none in

Table 1 The published cohort of proliferative verrucous leukoplakia (PVL)

Author	Patients	Mean age (years)	Gender M/F	Tobacco		Location			Treatment			Mean follow-up	Malignant transformation			Recurrences (%)
				Cases	Percentage		Cases	Percentage		Cases	Percentage	Years		Cases	Percentage	
Hansen *et al*, 1985	30	66	6/24	18	62	Buccal mucosa	23	76.6	Radiation	18	60	6.1	VC	9	30	90
						Hard soft palatal	18	60	Surgery	17	56.6		PSCC	12	40	
						Alveolar mucosa	16	53.03	Chemotherapy	6	20		SCC	5	16.6	
						Tongue	15	50	Multiple biopsies	5	16,6					
						Floor mouth	8	26.6	Laser	4	13.3					
						Gingiva	5	16.6	Retinoids	2	6.6					
						Lip	4	13.3	Others	2	6.6					
									None	2	6.6					
Zakrzewska *et al*, 1996	10	64	5/5	5	50	Buccal mucosa	8	80	Radiation	1	10	7.5	VC	4	40	90
						Hard palate	2	20	Surgery	6	60		PSCC	2	20	
						Soft palatal	1	10	Chemotherapy	1	10		SCC	4	40	
						Fauces	2	20	Laser	7	70					
						Gingival	8	80	Photodynamic	5	50					
						Tongue	6	60								
						Lip	2	20								
Silverman and Gorsky, 1997	54	62	11/43	17	31	Buccal mucosa	31	57	Surgery	42	77	11.6	SCC	38	70.3	85
						Palate	19	35	Surgery and Radiation	11	20.3					
						Tongue	29	54								
						Floor mouth	22	41								
						Gingiva	29	54								
						Lip	9	17								
Fettig *et al*, 2000	10	65	6/4	3	37.5	Gingiva	10	100	Simple excision	8	80	5	VC	3	30	100
						Floor mouth	1	10	Stripping	1	10		PSCC	1	10	
									Laser	5	50		SCC	4	40	
									Resección	3	30					
									Maxillectomy	2	20					
Bagan *et al*, 2003	30	71	6/24	7	23.3	Upper gingiva	23	76.7	Surgery	24	80	4.70	VC	8	26.7	86.7
						Lower gingival	26	86.7	Laser	28	60		SCC	19	63.3	
						Hard palate	15	50								
						Soft palate	4	13.3								
						Right buccal mucosa	17	56.7								
						Left buccal mucosa	17	56.7								
						Dorsum tongue	12	40								
						Ventral tongue	13	43.3								
						Upper lip	7	23.3								
						Lower lip	8	26.3								
Campisi *et al*, 2004	58	66	22/36	17	29.3	Non-reported			Non-reported			Non-reported	VC	3	5.1	Non-reported
													SCC	22	37.9	
Gandolfo *et al*, 2009	47	65.9	10/37	17	36.8	Alveolar crest	41	87.2	Non-reported			6.89	VC	9	19.1	
						Hard palate	20	42.6					SCC	32	68	
						Soft palate	14	29.8								
						Tongue	19	40.4								
						Floor	8	17								
						Buccal mucosa	336	70.2								
						Lip		12.8								

M, male; F, female; VC, verrucous carcinoma; SCC, squamous cell carcinoma; PSCC, papillary squamous cell carcinoma.

controls, again supporting an association of PVL with HPV. Some have found HPV both in PVL and in other leukoplakias. Campisi *et al* (2004) analyzed 58 cases with PVL and 90 oral leukoplakia (OL) cases, studying exfoliated lesional cells by nested PCR, and found HPV-DNA in 24.1% of PVL and in 25.5% of OL, with no statistical difference between both groups. In contrast, other authors did not find any association between PVL and HPV. Using polymerase chain reaction (PCR), Fettig *et al* (2000) found that none of their 10 PVL cases was positive for HPV. We did not find an association between PVL and HPV (Bagan *et al*, 2007).

Epstein–Barr virus (EBV) was examined by nested PCR in 10 cases of PVL, five with OSCC, and five normal mucosa samples. Epstein–Barr virus was detected in 60% of the PVL cases and in 40% of OSCC, but in none of the normal mucosa samples (Bagan *et al*, 2008). These preliminary results should be confirmed in other series.

Genetic studies

Aberrations in the cell cycle regulatory genes p16INK4a and p14ARF, with homozygous deletion, loss of heterozygosity, and mutation appear to be frequent findings in 20 PVL cases (Kresty *et al*, 2008). Histopathology and DNA ploidy have been suggested as useful in predicting the site of malignant transformation in PVL (Klanrit *et al*, 2007), but Olofsson (2007) drew attention to concern about the validity of data underlying the ploidy technique.

Diagnosis

The diagnosis of PVL based on clinical data is often late, as the progressive evolution of the lesions from homogeneous leukoplakic areas spreading to many different locations and with the appearance of erythroplastic and verrucous forms takes time. Histopathology may help, but features vary greatly depending on the site biopsied, the stage of the disease, and presumably by other factors. Hansen *et al* (1985) reported that PVL contained areas that ranged from simple hyperkeratosis to oral squamous cell carcinoma. Batsakis *et al* (1999) similarly described finding areas of verrucous hyperplasia, others with some degree of dysplasia, and others that were areas of squamous cell carcinoma.

Murrah and Batsakis (1994) and Batsakis *et al* (1999) proposed four stages of development: hyperkeratosis without epithelial dysplasia, verrucous hyperplasia, verrucous carcinoma, and conventional cell carcinoma.

Management

There is a lack of randomized controlled studies on PVL, and the published data are from series of retrospective cases or case reports only. There is no reliably effective management reported, and many of the lesions recur after treatment. Schoelch *et al* (1999) reported laser treatment using CO_2 and Nd:YAG lasers, but found a high rate of recurrences (83%). In our series of 30 cases (Bagan *et al*, 2003), the recurrence rate was comparable, at 86.7% after treatment with CO_2 laser and/or scalpel surgery. Fettig *et al* (2000) also found that the lesions recurred after conservative scalpel or laser excision, and many developed into verrucous or oral squamous cell carcinoma. Zakrzewska *et al* (1996) also managed some of their patients with PVL by photodynamic therapy.

Femiano *et al* (2001) reported an open trial of surgery in 25 cases with PVL compared with another 25 cases treated with surgery and the antiviral methisoprinol when the methisoprinol appeared to offer a significant benefit, but these results have yet to be confirmed in other studies.

Lesions were managed with surgery, carbon dioxide laser, and photodynamic therapy.

Evolution

Proliferative verrucous leukoplakia is characterized not only by a high rate of recurrences after treatment but also by malignant transformation in nearly 74% of cases, with a tendency for several oral cancers to appear (Cabay *et al*, 2007). Hansen *et al* (1985) reported that thirteen out of 30 cases died from the disease, 14 were alive with PLV lesions, and three were alive without signs of PVL.

Saito *et al* (1999) studied and compared the widespread oral leukoplakias and the localized ones. They found that the widespread multiple oral leukoplakias have a higher potential for the development of cancer than the localized lesions. Most of the multiple oral leukoplakias probably are Proliferative verrucous leukoplakias.

Silverman and Gorsky (1997) presented the clinical course and outcomes in 54 cases, some of whom were from the initial series published by Hansen *et al*, 1985; and 21 of the patients died from oral squamous cell carcinomas. Zakrzewska *et al* (1996) presented 10 cases of PVL: at first biopsy, no lesion was more serious than verrucous hyperplasia but eventually all developed oral squamous cell carcinomas. We studied 30 patients with PVL (Bagan *et al*, 2003) for the clinical aspects and characteristics focusing on their recurrences, the appearance of new lesions, and the frequency of development of oral cancer. We found recurrences after treatment in 86.7% of cases, new lesions during follow up in 83.3%, and oral cancer eventually in 63.3%, with a high incidence on the gingivae.

Proliferative verrucous leukoplakia is an unknown disease in which no etiological factor have been proven until today. The diagnostic criteria are not well established, and many patients are diagnosed many years after the first presentation of the disease, mostly retrospectively. There is a need to reach a consensus on these diagnostic criteria to be followed by most of the researchers and then there will be a large number of published series. The main topic on the disease is the high rate of malignant transformation, the lack of a success treatment, and the number of recurrences after management.

Author contributions

Jose Bagan and Crispian Scully wrote and designed the article. Yolanda Jimenez and Miguel Martorell carried out the literature review.

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