Oral verrucous lesions – a search for PVL

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ABSTRACT

Background. Proliferative verrucous leukoplakia (PVL) is a disease of extensive or multifocal verrucous-like lesions that has a high risk of recurrence and malignant transformation into a carcinoma. Verrucous hyperplasia (VH) is the histopathological finding most likely representing part of the PVL diagnosis. The objective of the present study was to update information on PVL and VH and critically evaluate the current diagnostic procedure of PVL.

Methods. A literature search on PubMed with terms covering PVL and VH was performed to identify papers published between the years 2000-2013. For comparison, the referrals of patients diagnosed with VH at our Department of Oral Pathology covering the same time period were evaluated.

Results. Fifty-four papers (1236 patients) fulfilled the inclusion criteria. At our department, 29 patients with VH were identified. In the literature, PVL was more common in females, on gingiva and with no history of tobacco use, contradictory to VH. In comparison, VH of our departmental patients was detected most commonly on the tongue and had a female predilection. Of the patients diagnosed with PVL, 47% developed a carcinoma. Only 5% and 3% of the patients with VH from the literature and from our department developed carcinoma.

Conclusion. PVL is its own disease entity while VH is a histologic diagnosis. As PVL is clinically verrucous, this feature should also be identified by histology. Thus, we now suggest that the PVL criteria should be modified as follows: a biopsy has confirmed the presence of VH. This modification would improve the diagnostics of PVL.

INTRODUCTION

In 1985 Hansen et al. described proliferative verrucous leukoplakia (PVL) as a long-term progressive condition, which develops initially as a white plaque of hyperkeratosis that eventually becomes a multifocal disease (1). Since then several improvements of the classification have been suggested. In 2010 Cerero-Lapiedra et al. proposed a new classification using a set of 6 major and 4 minor criteria (2). One of the six major criteria is the histology of the lesion including the following categories as follows: simple epithelial hyperkeratosis to verrucous hyperplasia (VH), verrucous carcinoma (VC), in situ carcinoma, or squamous cell carcinoma (SCC) (2). In 2013 Carrard et al. suggested simplifying Cerero-Lapiedra's classification by omitting the major and minor criteria in their modified classification: the diagnosis of PVL requires the involvement of the lesions in more than two oral subsites, a total added size of the leukoplakic areas of at least 3 cm, and a well-documented period of at least five years of disease evolution being characterized by spreading and the occurrence of one or more recurrences in a previously treated area (3). The temporal clinical evolution of PVL has been proposed to follow four stages according to Gillenwater et al. (2013): 1) one or more early focal presentations on the oral mucosa; 2) enlargement and spread over time (geographic expansion); 3) development of a verrucous appearance; 4) development of oral SCC (4).

PVL often resists attempts at therapy and has a high rate of recurrence and malignancy to VC and to invasive SCC (4,5,6,7,8). Because of the aggressiveness of PVL toward malignancy, early detection and careful follow-up of the lesion is essential. However, early detection is not straightforward. Even though PVL is a distinct clinical diagnosis, it is at the same time an elusive lesion. It is in fact impossible to distinguish the early presentation of PVL from other leukoplakias, especially the more conventional multifocal leukoplakia, either grossly or microscopically. Therefore the diagnosis of PVL can only be made through the careful observation of the temporal clinicopathologic evolution of the lesion. (4,9)

An additional difficulty with the diagnosis of PVL is that it is a clinical diagnosis that encompasses a spectrum of different clinical and histopathological stages. The histology of PVL is varied and the spectrum of PVL encompasses stages beginning from benign hyperplasia to VH followed by VC (1,2,4). These verrucous lesions are in themselves diagnostically challenging and the terminology is confusing. For example VH and VC can be impossible to distinguish from each other clinically and it is also challenging histologically (10). VH is a histological term that describes an exophytic overgrowth of well-differentiated

keratinized epithelium that is similar to VC but without the destructive, pushing border at its interface with the underlying connective tissue (11). Areas of VH may be encountered in association with VC, SCC or PVL (11).

The present study had two aims. First, to review all published cases including also case reports on PVL or VH to enlighten their most characteristic features and similarities. So far, systematic reviews have been done either on PVL or VH, separately. Also case reports have been mostly excluded in earlier reviews (5,6,8). Second, to evaluate single cases diagnosed with VH from the files of the Department of Oral Pathology, University of Turku, Turku, Finland, most likely representing the biopsy samples derived from PVL patients.

MATERIAL AND METHODS

Literature review. A PubMed-search was conducted using the following terms: proliferative verrucous leukoplakia, verrucous hyperplasia, verrucous dysplasia and verrucous papillary lesions. The papers on PVL and VH published in the year 2000 onwards until December 2013 were included. Additional papers were identified by reviewing the reference lists of the included papers. The inclusion criterion of the papers was that at least one record on the PVL or VH patient existed (e.g. site of lesion or follow-up data). Exclusion criteria were the following: studies not found through PubMed, studies in a language other than English, and studies not peer reviewed. Table 1 shows the characteristics of the patients and the lesions.

When summarizing the data from the different articles, the following information was given. When possible, the site of the lesions was reported at the beginning of follow-up. When reporting malignant transformation, if a patient had both VC and SCC, only SCC was noted. In addition, information on malignant transformation included both data on malignant transformation at the beginning, during and/or at the end of follow-up. The following studies included patients with malignancy already at the base line: 19, 20, 27, 28, 29, 30, 32, 38.

The Turku patients. A single institute material of patients with the histological diagnosis of VH during the years 2000-2013, most likely representing the patients with PVL, was collected at the Department of Oral Pathology, Institute of Dentistry, University of Turku, Turku, Finland, and referred to here as the Turku patients. The exclusion criteria were any previous or current VC or SCC in the oral cavity. The clinical information was collected from the pathologic anatomical diagnoses (PAD) without the information to allow the identification of the person. Therefore there was no need for ethical approval from our institute. Similarly, the follow-up after the VH diagnosis was performed as a search from the institute PAD referrals database to see if the patient had any additional PAD-diagnosis from a later date until the end of October 2014 (minimum of 10 months of follow-up).

RESULTS

Literature review: PVL. The PubMed-search on PVL resulted in 32 papers that fulfilled the inclusion criteria as outlined in the materials and methods (Table 1). Forty-seven percent of the papers were case reports with only one patient. The number of the patients varied from 3 to 58 patients in the rest of the papers.

Totally, 388 PVL patients were identified. The patients' characteristics together with their PVL data were summarized in Table 3. The female to male ratio was 2.2:1. The mean age of the patients was 64 years with a range of 40–84 years. Data on smoking status was available in 75% (292/388) of the patients. Of them 30% (88/292) were smokers or tobacco chewers. Information on malignant transformation of PVL was given for 94% (366/388) patients: 47% (173/366) of them were reported to have lesions that progressed either to VC, carcinoma in situ (CIS) or SCC.

The lesions were extensive or multifocal by their nature, and the site of the lesions was given for 77% (300/388) of the patients. There was no specific oral site for PVL. The localization in decreasing order was as follows: the gingiva (59%), the buccal mucosa (47%), the tongue (44%), the palate (31%), the alveolar crest (21%), the lip (9%) and the oral floor (8%). The site of the lesions was missing in 88 patients (23%).

Literature review: VH. Twenty-one papers on VH patients were included (Table 1). None of the papers were single case reports. Totally 848 patients with VH were identified in these papers. The number of patients per paper ranged from 5 to 324 with a mean of 44 patients. Some of the papers mentioned that individual patients were reported in several papers (20, 21, 22, 23). When possible, the data of these patients was included only once when that data was summarized in the present study (Table 3).

The female to male ratio was 1:3.8. The age of the patients ranged from 46 years to 62 years with a mean age of 54 years. Data on smoking status was available in 78% (663/848) of the patients and 83% (552/663) of them were reported to smoke or chew tobacco. Information on malignant transformation of VH was given for 62% (525/848): only 5% (25/525) of the VH progressed to VC or SCC with a range of 0–20% in the individual papers.

The location of the lesions was given for 61% (519/848) of the patients. The vast majority of the VH cases were seen on the buccal mucosa (51%) followed by the gingiva (10%), the

tongue (13%), the lip (12%), the palate (7%), the floor of the mouth (5%), and the alveolar crest (0.5%).

Combined PVL + VH literature review. When combining the separately described data on PVL and VH, there were altogether 1236 patients and the female to male ratio was 1:1.3. Altogether, 67 % (640/955) were reported as tobacco users and malignant transformation of the lesions was reported in 22% (196/1891).

Information on the site of the lesions was given for 59% (730/1236) of the patients. The main sites were the buccal mucosa (50%), the gingiva (31%) and the tongue (26%) followed by the palate (17%), the lip (11%), the alveolar crest (9%) and the floor of the mouth (6%).

The Turku patients. Totally, 29 patients diagnosed with VH were identified at the Department of Oral Pathology, Turku, Finland during the years 2000-2013 (Table 2, 3). The female to male ratio was 1.4:1. The age of the patients ranged from 11 years to 87 years and the mean age was 59 years. In only 8 cases out of 29, the information of smoking was included in the PAD referral letter and 6 of them were reported to smoke or chew tobacco. According to the PAD referrals to our institute between 2000-2014, only one VH lesion progressed to VC after 27 months follow-up resulting in a malignancy rate of 3% in the whole group of 29 patients (Table 2, ID 14). The site of the lesions in the declining order was as follows: the tongue (48%), the buccal mucosa (34%), the alveolar crest (24%), the lip (17%), the palate (10%), the floor of mouth (10%), and the gingiva (7%).

Comparison of the literature review and the Turku patients' material. The Turku VH cases were both similar and different from the PVL and VH cases presented in the literature in regards to gender distribution, site of lesions and malignant transformation. The Turku patients with VH showed a predilection for females, which was similar to the PVL cases from the literature but not to the VH patients from the literature. The tongue was the most affected site of the Turku VH patients as compared to the gingiva and the buccal mucosa in the PVL and VH patients derived from the literature, respectively. However, the buccal mucosa was the second most affected site for the Turku VH patients, too. The most obvious difference between the Turku VH patients and those described in the literature was the rate of malignant transformation; only one of our departmental patients was diagnosed with VC.

DISCUSSION

VH can be the histological diagnosis of a biopsy sample from a PVL lesion although WHO classifies them all as PVL (65). According to the present study and systematic review of the literature, VH and PVL have their own distinct features 1) PVL is more likely to affect women than men whereas VH is more likely in men than in women. 2) Tobacco use is common in VH patients as 83% had a history of using tobacco products while only 30% of PVL patients had a history of tobacco use. 3) PVL has a high rate of malignant transformation as 47% of the patients developed a VC or SCC. VH presented with a low rate of malignant transformation as only 5 % of the lesions progressed to VC or SCC. This progression rate is similar to that found in leukoplakias in general. Approximately 0.13-17.5% of leukoplakias progress to malignancy during ten years of follow-up (66).

The number of patients in the individual papers was not an inclusion criterion for the present study and almost half of the papers on PVL were actually case reports with only one case. More of the reported cases were covered when including also these case reports, unlike a recent review where only papers with 10 or more cases were included (8). Case studies can, however, bias the data as they usually describe clinically challenging cases and cases with malignant transformation. On the other hand, they can present the whole clinical spectrum of the disease. Only data since the year 2000 was included to present cases that are diagnosed in a similar way according to the criteria of these two disease entities and treated accordingly.

In the present study, a clear predilection for PVL in women was shown (2.4:1) as reported also previously (4,5,6,8). Interestingly, a similar predilection in women was found also in the Turku patients diagnosed with VH, contradictory to that found in the VH patients from the literature. One explanation may be that the VH patients from the literature were more often smokers and smoking is more prevalent in men.

In the present study, the majority of the PVL and VH patients from the literature had lesions on the gingiva and the buccal mucosa respectively, while the Turku patients had their VH lesions most frequently on the tongue. A few previous reviews have shown that the buccal mucosa and the tongue are the most affected sites for PVL (4,6). This difference between the reviews in the most affected site for PVL may be because of the different time periods, the literature review in the present study focusing on the most recent papers starting from the year 2000 onward while the previous reviews included papers before the year 2000. However, the

recent systematic review from Pentenero et al. found that 62.7% of the cases affect the gingiva, which is similar with the finding in the present study (59%) (8).

The present study showed that 47% of PVLs from the literature progressed to carcinoma. This is less than reported by Cabay et al. who found that 74% of the PVL progressed to carcinoma (6). Pentenero et al. who also included older papers than in the present study but only those with 10 or more patients, reported progression to malignancy in 60.7% of the PVL during 7.4-year follow-up (8). This indicates that reviews like ours including also case reports do not present only the cases with worse prognosis. Another explanation is that the lower malignant progression found by this study is due to the more advanced treatment modalities since all reports from the 20th century were excluded.

Interestingly, only one of the Turku patients with VH progressed to VC. No progression to SCC was reported. Since the PAD referral letters were collected from the archives of the Department of Oral Pathology, all prospective information on the patients with recurrence/progression of the disease was not available. This might explain the low number of malignant progression in the Turku patients. Another explanation is that based on the histology of biopsy samples we – as pathologists - are keen to ask the clinicians to keep the patients with VH in close follow-up. Thus, both the schedule of follow-up and treatment mode are of crucial importance. This study, however, excludes the role of treatment in the outcome of the lesions, since the data was available only for a minority of the patients in the literature review and not at all for the Turku patients.

One major difficulty when comparing the frequency of malignant transformation of PVL or VH in different studies is the inclusion criteria of the patients. For example, malignancy was an inclusion criteria for Klanrit et al. while Fettig et al. excluded all patients, who presented malignancy of the oral cavity at the baseline of the follow-up (32,24).

Field cancerization is often evident in patients with PVL progressing to carcinomas. Bagan et al. showed that more than 50% of the patients that developed a SCC also developed at least one additional primary SCC (16). Gandolfo et al. showed that 42% developed an additional primary tumor, and Ghazali et al. showed that 44% developed multifocal SCC (25,27). In the review by the Pentenero et al., the second primary tumor was reported in 37.2% of the patients (8).

In the present study the majority of the patients with PVL from the literature were treated with surgery (67%, 138/205) and laser (32%, 64/205). Similarly, also the patients with VH were

treated with surgery (60%, 211/352). In addition, photodynamic therapy was also used to treat 26% (92/352) of the patients with VH. Surgery is considered the preferred treatment of PVL, but because of the high recurrence rate there is no consensus on the most efficient and effective treatment mode of PVL (67). Photodynamic therapy has been shown effective for VH but more studies are needed (45,47,48,58,63).

Gathering data on PVL and VH for the systematic review in the present study was challenging. The major challenge was the terminology of both PVL and VH, in many cases most likely presenting the same course of disease. Furthermore, Mete et al suggests that PVL is under-diagnosed instead of over-diagnosed because there are no specific histological features in PVL (33). Because of this diagnostic confusion, there has recently been an attempt to propose clear diagnostic criteria for PVL (2, 3). Cerero-Lapiedra et al. proposed diagnostic criteria for PVL using a set of major and minor criteria (2). Carrard et al. simplified these criteria as given below (3).

1) leukoplakia with verrucous or wartlike areas that involve more than two oral subsites
2) at least 3 cm in size when adding all involved sites
3) evolution of lesion through spreading, enlarging and recurrence during a recorded history of at least five years
4) a biopsy has ruled out VC and SCC

These diagnostic criteria have been retrospectively evaluated as a useful tool (68).

One has to note that PVL is rather a clinical term of the disease entity while VH describes only the histology of the lesion. As already proposed by Hansen et al. in 1985, the spectrum of the histological findings is the major finding of the lesion of interest and VH may refer to a lesion that should be considered as an irreversible precursor to VC (1). All this might explain the confusion in the literature. Based on the present study and our experience in the field, we suggest that VH should be kept as a histologic diagnosis as such.

As the histology of the PVL lesion is the most critical issue in determining the treatment and even outcome of the lesions, we suggest that the 4th criteria in Carrard et al.'s classification should be more clearly defined (3). The major question is that since PVL is clinically defined as a verrucous lesion, should this "phenotype" be confirmed by histology. If so, the histologic criteria should be that of VH as classified by Pindborg et al.: VH is an exophytic overgrowth of well-differentiated keratinized epithelium that is similar to VC but without the destructive, pushing border at its interface with the underlying connective tissue (11). Thus, we now

suggest that the 4th criteria should be modified as follows: a biopsy has ruled out VC and SCC and confirmed the presence of VH in at least one of the possible multiple biopsies.

By using this suggested modification, the clinicians have less difficulty in settling the diagnosis of PVL. Once again the close follow-up of patients clinically but also including biopsy sampling will result in early detection of malignant transformation either to VC or SCC. As long as the etiology and etiopathogenesis is not known, no disease specific treatment is available. Furthermore, whether there are several etiological factors causing slightly different PVL was not possible to determine. Maybe in the future PVLs could be categorized at least into three groups by etiology: 1) PVL prone to progress to verrucous carcinoma, 2) PVL prone to progress to squamous cell carcinoma and 3) PVL without any risk to malignant transformation. Also research to identify the etiologic factors of PVL is highly warranted to design disease specific treatment in the future.

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Table 1. Summary of the patients with PVL and VH extracted from the literature

Reference	N (patient)	Sex F/M	Age at diagnosis (mean yrs)	N (lesions)	Site (all individual lesions)								Smoking (S)& Alcohol use (A)	Treatment	Follow-up time (mean, yrs)	Recurrence	VC	SCC	Malignant transformation % (VC+SCC)
					Gingiva	Buccal	Tongue	Palate	Alveolar crest	Lip/labial mucosa	Floor of mouth	Other							
Proliferative verrucous leukoplakia																			
Arsenic & Kurrer, 2013 (12)	12	4 / 8	57	NA	NA								NA	NA	NA	NA	NA	12	100
Bagan et al., 2011 (13)	55	36 / 19	62	s, m	49	26	27	15		4			20 S(s)/S(t)	34 L 27 S NA R	7.5	85% REC	0	27	49
Bagan et al., 2008 (14)	10	10 F	72	NA	10	6	8	4					NA	NA	NA	NA	1	5	60
Bagan et al., 2007 (15)	13	13 F	68	NA	13	9	7	7		1	1		3 S(s)/S(t)	NA	NA	NA	0	8	62
Bagan et al., 2004; 2003 (16,17)	30	24 / 6	71	m	30	30	25*	19*		15*			7 S(s)	18 L 24 S	4.7	26 REC 25 NL	8	19	90*
Campisi et al., 2004 (18)	58	36 / 22	67	s, m	NA								17 S(s) 10 A	NA	NA	NA	3	22	43
Chainani-Wu et al., 2013 (19)	1	1 M	46	e			1						1 S(s) 0 A	1 L	12	1 DF	0	1	100
Dal Vechio et al., 2012 (20)	1	1 F	76	1			1						0	1 L 1 S	0.5	1 DF	0	1	100
Del Vecchio et al., 2013 (21)	1	1 F	84	e		1							0	1 P	1.5	1 DF	0	0	0
Feller et al., 2006 (22)	1	1 M	40	m				1	1				1 S(s) 0 A	1 NT	0.3	0	0	0	0

Femiano et al., 2001 (23)	50	30 / 20	53 **	s, m	18	9	16	8	2		5	4	NA	25 tM 50 S	1.5	22 REC 28 DF	0	0	0
Fettig et al., 2000 (24)	10	4 / 6	65	s	10						1		3 S(s) 2 NA	5 L 8 S	4.4	10 REC	2	4	60
Gandolfo et al., 2009 (25)	47	37 / 10	66	s, m	22	33	19	25	41	6	8		17 S(s) 12 A	NA	6.9	NA	9 ***	32 ***	40
Ge et al., 2011 (26)	1	1 F	52	m	1	1	1	1				1	NA	1 tM 1 S	0.3	0	0	1 Cis	100
Ghazali et al., 2003 (27)	9	7 / 2	62	m	6	5	3	1			1	5	1 S(s) 4 S(t) 1 A	1 L 9 S	4.7	5 REC	4	6	78
Gouvea et al., 2013 (28)	21	18 / 3	66	m	2*	4*	9*		5	1			0	NA	7.4	NA	2	7	43
Gouvea et al., 2010 (29)	1	1 F	64	e			1						0	1 S 1 R 1 Ch	3.8	1 REC	0	1	100
Gouvea et al., 2010 (30)	12	12 F	70	s, m	4	5	6	2	8	2	3	2	3 S(s) 3 A	4 S 2 R	5.8 **	NA	1	3	33
Issrani et al., 2013 (31)	1	1 M	60	3					1	1		1	1 S(t)	1 S	0	NA	NA	NA	NA
Klanrit et al., 2007 (32)	6	5 / 1	66	m	4	3	2	3	4	1		2	2 S(s) 2 A 1 NA	1 L 6 S	12-25 range	REC	0	6	100
Kresty et al., 2008 (33)	20	12 / 8	61	NA	4	5	1	4			1	5	NA	NA	NA	NA	NA	NA	NA
Lopes et al., 2000 (34)	1	1 M	57	e			1				1		1 S(s)	1 tM 1 L 1 S	1.8 *	1 REC 1 NL	1	0	100
Lopez-Jornet & Alonso 2008 (35)	1	1 F	70	m	NA								NA	1 NT	10	0	0	1 Cis	100

Mergoni et al., 2011 (36)	1	1 M	58	m	1	1							0 S(s)	1 M 1 L	7	1 REC	0	0	0
Mete et al., 2010 (37)	1	1 F	59	e			1						0 S(s)	1 S	NA	0	0	0	0
Morton et al., 2007 (38)	3	2 / 1	80	NA	2	1		1				1	1 S(s)	3 S	3.7	2 REC	1	2	100
Navarro et al., 2004 (39)	1	1 M	78	m			1				1		1 S(s)	1 S	10	1 REC	0	1	100
Poveda-Roda et al., 2010 (40)	17	10 / 7	61	m	NA								6 S(s)	6 tM 12 sM	0.5	17 NC	0	2	12
Shopper et al., 2004 (41)	1	1 F	48	m	1	1	1	1			1		0	NA	4*	NA	0	1	100
Singh et al., 2012 (42)	1	1 M	56	1		1						1	0 S(s)	NA	NA	NA	NA	NA	NA
Vigliante et al., 2003 (43)	1	1 F	65	m, e	1	1							0	1 tM 1 sM 1 L 1 S 1 Ch 1 R	7	1 REC	0	1	100
Verrucous hyperplasia																			
Chang et al, 2002 (44)	57	NA	NA	s, m		35							NA	NA	NA	NA	NA	NA	NA
Chen HM et al., 2007 **** (45)	24	24 M	52	s, m		15		1	1	7			24 S(s) 24 S(t)	24 P	1.3	24 DF	0	0	0
Chen HM et al., 2005 (46)	15	NA	NA	s, m		10		1		4			15 S(s) 15 S(t)	NA	NA	NA	NA	NA	NA
Chen HM et al., 2005 (47)	8	8 M	50	s, m		6				2			8 S(s) 8 S(t)	8 P	0.9	8 DF	0	0	0
Chen HM et al., 2004 (48)	5	5 M	52	s, m		1				2		2	5 S(s) 5 S(t)	5 P	0.5	5 DF	0	0	0

Chen YK et al., 2002; 2002 (49,50)	20	20 M	NA	NA		20							20 S(t)	NA	2	NA	0	4	20
Hazarey et al., 2011 (51)	19	6 / 13	50	NA		11							13 S(s)/S(t)	2 L 13 S	NA	2 REC	0	0	0
Ho et al., 2009 (52)	44	44 M	47	NA	NA								NA	NT	3.5	NA	0	9	20
Hsieh et al., 2010 (53)	11	11 M	46	NA		4		1		4		2	11 S(s) 11 S(t) 11 A	NA	NA	NA	NA	NA	NA
Hsue et al., 2007 (54)	324	NA	NA	NA	NA								324 S(s) 324 S(t) 324 A	NA	4.6	NA	2	8	3
Klieb et al., 2007 (55)	28	15 / 13	61	NA	19	5	1	1				2	NA	NA	NA	NA	NA	NA	NA
Lee et al., 2013 (56)	11	NA	NA	NA	1	5	2						NA	NA	NA	NA	NA	NA	NA
Lin et al., 2011 (57)	30	1 / 29	47	NA	2	21		2		3	2		29 S(s) 26 S(t) 18 A	30 S	NA	NA	NA	NA	NA
Lin et al., 2010 (58)	40	1 / 39	50	NA		25	5	5		4	1		NA	40 P	1.7	40 DF	0	0	0
Poh et al., 2001 (59)	25	14 / 11	62	NA	NA								17 S(s)	NA	NA	NA	NA	NA	NA
Tsai et al., 2004 (60)	5	NA	NA	NA	NA								NA	5 P	NA	4 DF	NA	NA	NA
Wang et al., 2009 ***** (61)	56	1 / 55	52	60	4	29	12	11		4			50 S(s) 51 S(t) 25 A	47 S 5 P 8 NT	4.9	5 DF	3 ***	3 ***	10
Yu et al., 2013 ****** (62)	18	1 / 17	47	s, m	2	11		2		3			17 S(s) 17 S(t)	18 P	NA	18 DF	0	0	0

Yu et al., 2008 **** (63)	36	1 / 35	51	s, m		24		3	1	8			35 S(s) 35 S(t)	36 P	2.2	36 DF	0	0	0
Zhu et al., 2012 (64)	12 1	51 / 70	59	NA	19	29	39	7		20	7		31 S(s) 34 A	121 S	NA	NA	NA	NA	NA

F = Female, M = Male,
s = single, m = multifocal, e = extensive
Other = eg vestibulum, retromolar area, oral commisure
S(s) = smoker/former smoker, S(t) = smokeless tobacco use/former use, A = any alcohol use
L = laser, S = surgery, R = radiotheraohy, P = topical 5-aminolevulinic acid-mediated photodynamic therapy, tM = topical medication including methisoprinol-therapy, retinoic acid, beta-carotene, bleomycin, sM = systemic retinoids, M = medical therapy not specified, Ch = Chemotherapy, NT = no treatment
REC = recurrence/(new lesion) of PVL, DF= disease free, NL = new lesions, NC = not curative
Cis = carcinoma in situ, VC = verrucous carcinoma, SCC = squamous cell carcinoma

* interpreted and/or combined data from the available data
** median instead of mean
*** number of lesions, not able to identify individual patients
**** 13 patients previously reported in 47, 48, 60
***** 5 patients previously reported in 63
****** all patients previously reported in 45, 47, 48, 58, 60, 63

Table 2. Patients diagnosed with VH during the years 2000-2013 at the Department of Oral Pathology, Institute of Dentistry, Faculty of Medicine, University of Turku, Turku, Finland.

Patient # in data	Sex	Age	Multiple lesions reported	Size of largest biopsied lesion, mm	Site of biopsy/excision	Smoking / Alcohol use	Follow-up time before biopsy (years)	Candidiasis	Dysplasia
1	F	40	-	NA	T	NA	NA	-	-
2a	F	38	+	10	Bc	NA	4.8	+	Mi
2b				10	T			-	Mi
3	M	53	+	NA	Lm	S	NA	-	-
4	M	64	-	NA	Bc	NA	1	+	Mi
5	M	62	-	10	F	NA	2.1	-	Mi
6	M	68	-	10	P	NA	NA	-	-
7 I	M	63	-	5	L	S	0.5	-	-
7 II	M	64	-	NA	L	S	1.2	-	-
7 III	M	69	-	5	T	S	6.1	-	-
8	F	55	-	6	T	NA	1	-	-
9	F	57	-	NA	T	S	NA	+	Mo
10	M	55	+	NA	B	NOS	NA	-	Mi
11	F	65	-	30	T	NA	NA	-	-
12	F	78	-	8	T	NA	NA	+	-
13 I	F	76	-	13	Bs	NA	2	-	-
13 II	F	76	-	NA	Bs	NA	2.1	-	Mo
14 I a	F	80	+	30	Bs	NOS / NOA	0.8	-	-
14 I b				NA	Lm			-	-
14 II	F	81	+	NA	AC	NOS / NOA	1	-	-
14 III a	F	81	+	20	AC	NOS / NOA	1.3	+	Mi
14 III b				35	B			+	Mi
14 III c				22	AC			+	Mi
14 IV	F	82	+	20	B, AC	NOS / NOA	1.9	-	-
14 V a	F	82	+	NA	AC	NOS / NOA	2.3	-	-
14 V b				NA	AC			-	Mo
15	M	60	-	8	P	S	NA	-	-
16	F	65	-	NA	F	NA	NA	-	-
17	F	60	-	10	P	NA	1	+	Mo
18	F	47	-	4	T	S	0.3	-	-

19	M	35	-	9	T	NA	NA	-	-
20	F	75	-	NA	AC	NA	0.5	-	Mi
21	F	76	-	10	T	NA	0.2	-	-
22	M	34	-	NA	T	NA	2	-	-
23	M	70	-	5	T	NA	NA	-	-
24	F	72	-	10	B	NA	NA	-	Mi
25	M	49	-	NA	T	NA	0.2	-	+
26 a	F	87	+	15	Lm	NA	NA	-	Mo
26 b				10	T			-	Mi
27	F	11	+	NA	B	NA	0.4	-	-
28	F	50	+	8	F	NA	NA	-	-
29	M	53	-	15	B, Bc	S	2	+	Mo

NA = data not available, + = yes, - = no
F = female, M = male,
T = tongue, B = buccal mucosa, Bc = buccal/oral commissure, Bs = buccal sulcus, L = lip, Lm = labial mucosa, F = floor of mouth, P = palate, G = gingiva, AC = alveolar crest,
S = smoker / former smoker, NOS = non-smoker, NOA = no alcohol consumption,
Mi = mild dysplasia, Mo = moderate dysplasia

number plus small letter = two biopsies taken at the same time from different areas
number plus roman number = biopsies taken at different time

Table 3. Pooled data on PVL and VH patients from the literature and data from the patients diagnosed with VH at the Department of Oral Pathology, Institute of Dentistry, Faculty of Medicine, University of Turku, Turku, Finland.

	PVL from literature	VH from literature	PVL + VH from literature	VH from institution
Total number of patients	388	848	1236	29
F/M-ratio	2.2:1	1:3.8	1:1.3	1.4:1
Tobacco users	30 % (88/292)	83 % (552/663)	67 % (640/955)	21% (6/29) *
Malignant transformation (VC + SCC)	47 % (173/366)	5 % (25/525)	22% (196/891)	3 % (1VC)
Gingiva	59% (178/300)	10% (45/430)	31% (223/730)	7% (2/29)
Buccal	47% (142/300)	51% (221/430)	50% (363/730)	34% (10/29)
Tongue	44% (131/300)	13% (58/430)	26% (189/730)	48% (14/29)
Palate	31% (92/300)	7% (31/430)	17% (123/730)	10% (3/29)
Alveolar Crest	21% (62/300)	0.5% (2/430)	9% (64/730)	24% (7/29)
Lip	9% (27/300)	12% (50/430)	11% (77/730)	17% (5/29)
Floor of mouth	8% (23/300)	5% (19/430)	6% (42/730)	10% (3/29)
Surgery	67% (138/205)	60% (211/352)	19% (65/348)	
Laser	31% (64/205)	0.6% (2/352)	19% (66/348)	
Topical Medication	17% (35/205)	0% (0/352)	10% (35/348)	
Photodynamic therapy	0,01% (1/205)	26% (92/352)	27% (93/348)	

* information on smoking status was not reported for all 30 patients: in addition to the 6 patients reported to smoke, 2 patients were reported not to smoke