Original Article

Exophytic verrucous hyperplasia in oral submucous fibrosis: A single-center study

Aakruti M Shah, Shivani Bansal, Pankaj M Shirsat, Pooja Prasad, Rajiv S Desai

Department of Oral Pathology, Nair Hospital Dental College, Mumbai, Maharashtra, India

Abstract

Introduction: The present study analyzed the occurrence of exophytic verrucous hyperplasia (EVH) in the background of oral submucous fibrosis (OSF), which presents clinically as a solitary verrucopapillary lesion (VPL) mimicking malignancy. We also aimed to obtain additional information on VELscope appearance and histopathological features of EVH.

Materials and Methods: The prevalence of EVH in OSF background was assessed from January 2014 to December 2018 using VELscope and histopathological examination.

Results: Six hundred and sixty-two OSF patients were examined. Thirteen patients presented with solitary VPL in OSF background. A VELscope examination found ten cases with increased autofluorescence (fluorescence visualization increase, FVI), two cases with autofluorescence loss (fluorescence visualization loss, FVL), whereas one case exhibited dual autofluorescence (focal areas of FVL within FVI regions). Histopathologic examination revealed two FVL cases as oral verrucous carcinoma (OVC) and oral squamous cell carcinoma (OSCC) and one dual autofluorescence case as OVC, while six FVI cases showed nondysplastic epithelium having verrucopapillary pattern without connective tissue invasion, consistent with the clinicopathological diagnosis of EVH.

Conclusion: The present study demonstrated the evidence of EVH in OSF background, which on histopathological examination revealed nondysplastic epithelium exhibiting the verrucopapillary pattern. A VELscope examination of these lesions showed increased autofluorescence, suggesting its nonneoplastic nature of clinically malignant-looking exophytic VPLs in OSF background. Present study suggests newer perspective for using the term oral verrucous hyperplasia (OVH) and EVH with justification and also proposes to introduce new terminology such as oral verrucous dysplasia and exophytic verrucous dysplasia.

Keywords: Exophytic verrucous dysplasia, exophytic verrucous hyperplasia, oral squamous cell carcinoma, oral submucous fibrosis, oral verrucous carcinoma, oral verrucous dysplasia, oral verrucous hyperplasia, VELscope, verrucopapillary lesion

Address for correspondence: Dr. Rajiv S Desai, Department of Oral Pathology, Nair Hospital Dental College, Mumbai - 400 008, Maharashtra, India.
E-mail: nansrd@hotmail.com

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INTRODUCTION

Oral submucous fibrosis (OSF) is a chronic, insidious, potentially malignant disorder, affecting the oral mucosa. It carries a high risk of malignant transformation rate in the range of 7%–13% and is strongly affiliated with areca nut chewing habit which is most prevalent among people of South Asian origin.[1]

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Exophytic verrucous hyperplasia (EVH) occurring in OSF environment is a newly described entity having a distinct clinicopathological presentation.[2,3] Albeit the highly suspicious clinical appearance, no histological confirmation of invasion was observed among these lesions.[4]

The use of autofluorescence as a diagnostic tool for cancer detection is based on the premise that naturally occurring fluorochromes located in the epithelium (e.g., nicotinamide adenine dinucleotide and flavin adenine dinucleotide) and submucosa (e.g., collagen and elastin) exhibit fluorescence in green spectral range when examined between the wavelengths 375 and 440 nm.[5-7] The VELscope (LED Medical Diagnostics Inc., Burnaby Canada) uses the same hypothesis to detect oral mucosal abnormalities by direct tissue autofluorescence.[8-10] When excited at wavelengths between 375 and 440 nm, healthy mucosa emits a pale green autofluorescence when viewed through a filter. The dysplastic tissues however appear darker compared to surrounding healthy tissue due to a disturbance in the distribution of the fluorochromes.[5]

The present study was conducted to report the occurrence of EVH in the background of OSF at our institute. We also aimed to obtain additional information on the autofluorescence characteristics of these lesions and correlate the same with histopathological findings to facilitate a better understanding of this entity, as it may have far-reaching implications on its management. The present study suggests newer perspective for using the term oral verrucous hyperplasia (OVH) and EVH with justification and also proposes to introduce new terminology such as oral verrucous dysplasia (OVD) and exophytic verrucous dysplasia (EVD).

MATERIALS AND METHODS

Six hundred and sixty-two OSF cases reported to the Department of Oral Pathology, over a period of 5 years (January 2014–December 2018) were included in the present study. Informed consent was obtained from the patients who voluntarily agreed to participate in the study. The study was approved by the Institutional Ethics Committee (EC-67/OPATH-07ND/2017). The study design was in accordance with the principles of Declaration of Helsinki and consistent with the guidelines of Good Clinical Practice as given by the International Conference on Harmonization.[11]

Conventional oral examination (COE) of six hundred and sixty-two patients with OSF was performed using incandescent operatory light. All the OSF cases were diagnosed on clinical grounds of restricted mouth opening and confirmed histologically.[1] Patients with exophytic verrucopapillary lesions (VPLs) mimicking malignancy in the background of OSF were a part of the present study. Following COE autofluorescence, examination of patients was conducted using VELscope (LED Medical Diagnostics Inc., Burnaby Canada). Photo documentation of all these VPLs was carried out during COE and VELscope examination for future comparison and analysis.

Based on the autofluorescence findings as per the manufacturer's literature, the lesions were divided into two groups. Group 1 included lesions that showed autofluorescence loss (fluorescence visualization loss or FVL), appearing dark compared to the surrounding unaffected tissue exhibiting pale green autofluorescence, thus indicative of a malignant or dysplastic change. Group 2 included lesions that showed autofluorescence retention (fluorescence visualization retained or FVR), similar to that of the surrounding healthy tissue. Only a total FVL was classified as malignant or dysplastic. Lesions demonstrating autofluorescence patterns apart from a complete FVL were included in the FVR group.[12] The sample size of 12 was determined using the formula:

$$n = \frac{\left(Z_{\alpha} + Z_{1-\beta}\right)^2 P\left(1-P\right)}{\delta^2}$$

After obtaining appropriate informed consent, the present study included only those VPLs, which underwent incisional biopsy first to rule out malignancy. Hematoxylin and eosin stained formalin-fixed paraffin-embedded tissue sections were assessed by two experienced oral pathologists who were blinded to the VELscope findings and were not a part of the clinical study. Malignant lesions were referred to cancer specialty center, while nonmalignant lesions were completely excised with clear margins. VELscope examination findings were correlated with the histopathological diagnosis. For detailing purpose, Group 2 lesions were further divided into four subgroups based on their autofluorescence findings as: Group 2A (FVR lesions), Group 2B (lesions with a combination of FVL and FVR), Group 2C (lesional area displaying increased autofluorescence compared to the surrounding tissue, labeled as fluorescence visualization increase or FVI) and Group 2D (lesions having a combined FVI and FVL).[12]

RESULTS

Six hundred and sixty-two OSF patients were examined during the study period of 5-year (January 2014–December 2018). Thirteen cases (1.96%) were clinically diagnosed as malignant-looking VPLs in the

background of OSF. They were solitary, white, exophytic verrucopapillary outgrowth, measuring about 2–3 cm in size, predominantly occurring in the buccal mucosa, masquerading as oral verrucous carcinoma (OVC) or oral squamous cell carcinoma (OSCC). No sign of induration was evident in all cases. Characteristically, all these thirteen cases were males, ranging from 19 to 63 years of age (mean age 40.2 years) [Table 1].

VELscope examination of these lesions exhibited loss of autofluorescence (Group 1, FVL) in two cases, while one lesion exhibited dual autofluorescence showing focal areas of FVL interspersed between FVI regions (Group 2D, lesions showing a combined FVI and FVL). Histopathological examination of two lesions exhibiting FVL included OVC ($n = 1$) and OSCC ($n = 1$), while that of dual autofluorescence was OVC ($n = 1$). These three lesions were not included in our study [Figure 1]. Only six patients of ten VPLs demonstrating increased autofluorescence (Group 2C, FVI) underwent biopsy procedure, which was included in the present study as four patients refused to undergo biopsy procedure [Figures 2 and 3]. Incisional biopsy of all these six lesions showed verrucous hyperplasia and thickened epithelium with keratin plugging in-between papillary projections with basal cell hyperplasia and acanthosis which was diagnostic of EVH. Surprisingly, none of these lesions revealed the presence of epithelial dysplasia or connective tissue invasion [Table 2]. Subsequently, excisional biopsy of all six lesions showed similar histopathological features as incisional biopsy, consistent with the initial diagnosis of EVH [Figure 4].

Based on clinicopathological criteria proposed by the working committee of the first Asian Regional Meeting on the terminology and criteria for VPLs of the oral cavity held at Kuala Lumpur, Malaysia, a final diagnosis of "EVH" was rendered for all the cases.[2,3] All the cases were lost to follow-up except one, which showed no signs of recurrence after 2 years [Figure 5].

DISCUSSION

Exophytic VPLs in the background of OSF are diagnostically challenging as they range from simple benign hyperplastic lesions to OVH to OVC and OSCC.[13] OVH seems to be an enigmatic lesion due to marked clinical and histological similarity to OVC.[14]

Various researchers have described and discussed OVH differently creating confusion regarding its use in clinical setting.[13-17] Shear and Pindborg[14] have classified OVH solely based on histopathological criteria as "sharp" and

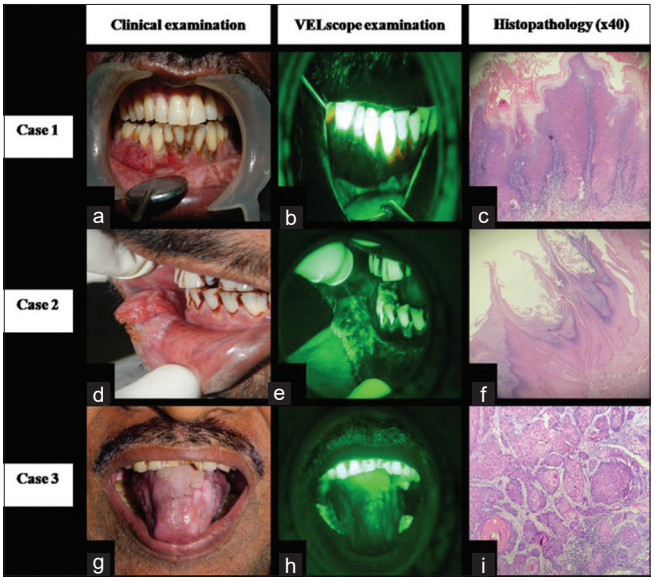

Figure 1: Exophytic malignant verrucopapillary lesion in oral submucous fibrosis background. (a, d and g) Clinical, (b and h), VELscope exhibiting FVL. (e) VELscope exhibiting a combination of FVI and FVL, (c and f) histopathology showing papillary projections with severe dysplasia (×40), (i) histopathology showing large invasive squamous islands with keratinous pearls inside (×40). FVI: Fluorescence visualization increase, FVL: Fluorescence visualization loss

Table 1: Clinicopathological features of verrucopapillary lesion mimicking malignancy in the background of oral submucous fibrosis

Case	Age (years), sex	Inter-incisal opening (mm)	Size of the lesion (cm)	Site of VPL	VELscope appearance	Histopathological diagnosis	Follow-up status
1	49/male	23	2×2	Right buccal gingiva	FVL	OVC	NA
2	35/male	26	2×2	Right commissure extending onto right buccal mucosa	Combination of FVI and FVL	OVC	NA
3	53/male	35	2×1.5	Left lateral border of tongue	FVL	OSCC	NA
4	36/male	20	3×1	Right buccal mucosa	FVI	EVH without dysplasia	NA
5	19/male	31	2×1	Maxillary right labial mucosa	FVI	EVH without dysplasia	2 years' follow-up-without recurrence
6	45/male	35	2×2	Right buccal mucosa	FVI	EVH without dysplasia	NA
7	49/male	28	5×4	Left buccal mucosa	FVI	EVH without dysplasia	NA
8	33/male	26	2×1	Left buccal mucosa	FVI	EVH without dysplasia	NA
9	50/male	40	2×1	Right buccal mucosa	FVI	EVH without dysplasia	NA

VPL: Verrucopapillary lesion, EVH: Exophytic verrucous hyperplasia, OVC: Oral verrucous carcinoma, OSCC: Oral squamous cell carcinoma, FVI: Fluorescence visualization increase, FVL: Fluorescence visualization loss, NA: Not available, VEL: Visually enhanced lesion

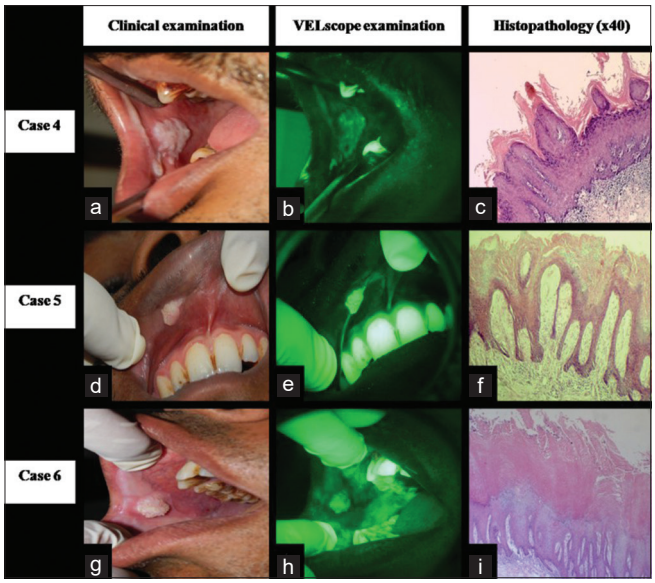

Figure 2: Exophytic verrucous hyperplasia in oral submucous fibrosis background. (a, d and g) Clinical, (b, e and h) VELscope exhibiting FVI, (c, f and i) histology showing papillary projections without dysplasia and invasion (×40). FVI: Fluorescence visualization increase

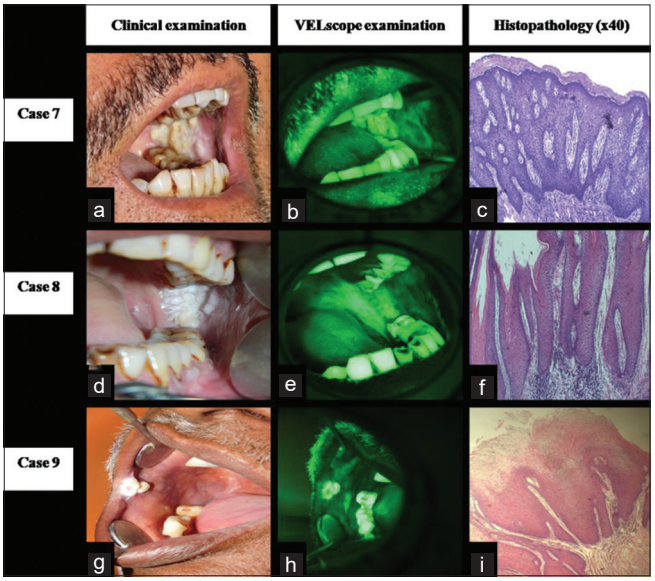

Figure 3: Exophytic verrucous hyperplasia in oral submucous fibrosis background. (a, d and g) Clinical, (b, e and h) VELscope exhibiting FVI, (c, f and i), histology showing papillary projections without dysplasia and invasion (×40). FVI: Fluorescence visualization increase

"blunt" variants, clinically indistinct from OVC. They observed the coexistence of OVH with OVC in 29% of their cases. Although Arendorf and Aldred[15] characterized OVH and OVC as histologically different, they opined OVH be considered as OVC until proven otherwise. Slootweg and Müller[16] did not consider OVH as a separate entity and considered it as a spectrum of OVC as they did not observe any major difference in clinical parameters including age and sex distribution. They also observed 25.8% of their cases to have coexisting OVH and OVC. Murrah and Batsakis[17] strictly reserve the term OVH to be used histopathologically and considered it be a precursor of OVC. Wang *et al*.[13] classified OVH histopathologically as "mass" and "plaque" type lesion, with former having higher malignant transformation rate. Both types were showing histological presence of dysplasia. They suggested the term OVH could be applied clinically and histopathologically only to "mass type lesions" and that the "plaque type lesions" be clinically termed oral verruciform leukoplakia. To bring uniformity in reporting these both clinically and histopathologically, a consensus report was published following the first Asian Regional Meeting on the Terminology and Criteria for VPLs of the Oral Cavity held in Kuala Lumpur, Malaysia. This expert group proposed clinicopathological criteria for the diagnosis of OVH. They proposed the term "EVH" to denote the clinical entity that represents the microscopic diagnosis of OVH.[2,3] The proposed clinical criteria for EVH include (i) lesions clinically appearing in two forms: (a) as an exophytic fleshy verrucopapillary outgrowth and (b) as a white plaque-like exophytic verrucous lesion, (ii) EVH can occur anywhere in the oral cavity and should be more than 1 cm in size, (iii) EVH is a discrete and solitary lesion, unlike proliferative verrucous leukoplakia (PVL), (iv) EVH may coexist in a patient presenting with OSF and (v) the absence of induration is a cardinal clinical feature when compared to OVC or OSCC.[2,3]

The proposed histological criteria for EVH include (i) the presence of keratin plugging into verruco-papillary processes, (ii) hyperplastic epithelium with basal cell hyperplasia and acanthosis, (iii) the absence of downward growth of the hyperplastic epithelium into the lamina propria, (iv) epithelial dysplasia may or may not present and (v) subepithelial lymphocytic infiltration as a host response may or may not be present.[2,3]

Patil *et al*. (2016)[18] reevaluated 188 VPLs using criteria established at the first Asian Regional Meeting on the Terminology and Criteria for VPLs of the Oral Cavity held in Kuala Lumpur, Malaysia.[2] They found 57 cases of OVH which included 26 cases of OVH without dysplasia and 31 cases with dysplasia.[18]

None of the above mentioned studies have observed OVH or EVH in OSF background. Although exophytic lesions in the background of OSF are not rare, reported data on this subject from South Asian countries are sparse, where OSF is highly prevalent.[4] Jayasinghe *et al*.[4] for the first time highlighted 5 cases of EVH, who presented with clinically malignant exophytic VPLs in the background of OSF.

Table 2: Histopathological features of verrucopapillary lesions in the background of oral submucous fibrosis

Histopathological criteria	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9
Keratinized verrucopapillary processes	+	+	+	+	+	+	+	+	+
Keratin plugs	+	+	+	+	+	+	+	+	+
Epithelial lining	Parakeratinized	Parakeratinized	Parakeratinized	Parakeratinized	Parakeratinized	Parakeratinized	Parakeratinized	Parakeratinized	Parakeratinized
Epithelial hyperplasia									
Basal cell hyperplasia	+	+	+	+	+	+	+	+	+
Acanthosis	+	+	+	+	+	+	+	+	+
Level of downward growth in comparison to adjacent normal epithelium (same/below/above)	Below	Below	Invasion	Same	Same	Same	Same	Same	Same
Epithelial dysplasia	Present	Present	Present	Absent	Absent	Absent	Absent	Absent	Absent
Subepithelial lymphocytic infiltrate	Mild	Mild	Moderate	Mild	Mild	Mild	Mild	Moderate	Mild
Diagnosis	OVC	OVC	OSCC	EVH	EVH	EVH	EVH	EVH	EVH
Cases excluded/included	Excluded	Excluded	Excluded	Included	Included	Included	Included	Included	Included

+: Present, OVC: Oral verrucous carcinoma, OSCC: Oral squamous cell carcinoma, EVH: Exophytic verrucous hyperplasia

We report a case series of six patients who presented with verrucopapillary exophytic lesions mimicking frank malignancy on clinical examination, giving altogether different histopathological finding. Histopathology of all six cases showed no evidence of dysplasia or invasion despite their size and exophytic appearance. All these patients were chronic betel nut chewers, and lesions were slowly growing for the last 2–3 years. Although our cases had a clinical presentation similar to Jayasinghe *et al*.,[4] histopathologically, we observed the absence of epithelial dysplasia in contrast to their findings, who reported mild to moderate epithelial dysplasia in their case series.

The question which should be raised in our cases is why and how the nondysplastic epithelium proliferates in an exophytic pattern mimicking conventional malignancy. In this regard, we endorse Jayasinghe *et al*.[4] views that the abnormally fibrosed connective tissue stroma of OSF may be resistant to the process of invasion allowing epithelium to proliferate in an exophytic pattern.

Even malignancy in OSF reported having a better prognosis since OSF may actually be a protective mechanism of the body as a result of fibrosis in response to areca nut use in any form.[19]

Various studies on OVH[13-17] and EVH[2-4,18] uniformly diagnosed OVH irrespective of the presence or absence of dysplasia. Findings of our present study provide evidence that OVH can occur without epithelial dysplasia. Hence, to avoid confusion, we suggest the term OVH and EVH for lesions not showing features of epithelial dysplasia whereas OVD and EVD be reserved for VPL associated with epithelial dysplasia. We preferred the term EVH specifically for the clinically malignant appearing exophytic lesions, histopathologically exhibiting verrucous hyperplasia without dysplasia. On the other hand, the term OVH should be restricted to lesions showing microscopic features of verrucous hyperplasia without dysplasia occurring in nonexophytic lesions like plaque-type leukoplakia revealing characteristic hyperplastic, proliferative epithelium. Similarly, the term OVD and EVD should be reserved for lesions showing microscopic verrucous hyperplastic features with dysplasia in nonexophytic and exophytic lesions, respectively. Thus, proposed EVH and EVD are clinicopathological terms with prognostic value against EVH as described by the first Asian Regional Meeting on the Terminology and Criteria for VPLs of the Oral Cavity held in Kuala Lumpur, Malaysia and OVH by Shear and Pindborg. Since the sample size is small, the suggestion of using two separate terms - EVH and EVD may be carried out later with sound evidence including larger sample size.

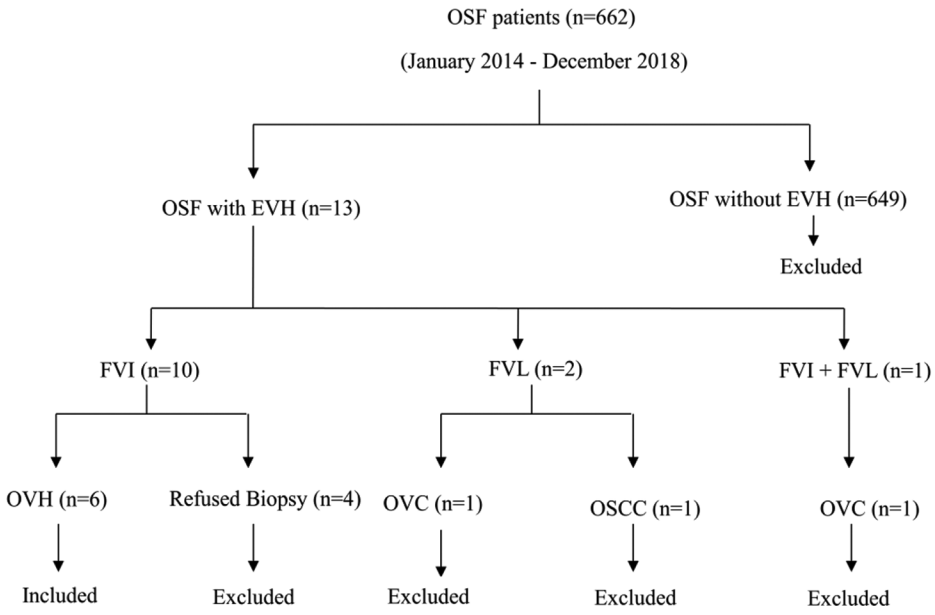

Figure 4: Flow chart showing patient inclusion criteria. EVH: Exophytic verrucous hyperplasia, OSF: Oral submucous fibrosis, FVI: Fluorescence visualization increase, FVL: Fluorescence visualization loss, OVH: Oral verrucous hyperplasia, OVC: Oral verrucous carcinoma, OSCC: Oral squamous cell carcinoma

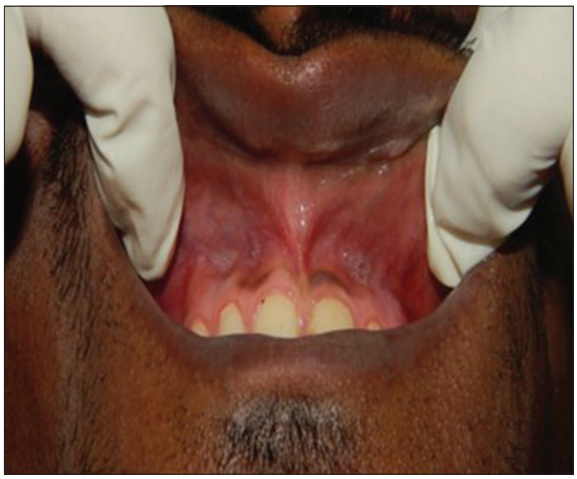

Figure 5: Two-year follow-up of case 5 showing no recurrence

We could present only six cases of EVH considering the rarity of lesion which could be a limitation of the study.

Frequent observation of presence of dysplasia in OVH cases (OVD) coexisiting with OVC[14,16,18] raises the question whether OVC could possibly be preceded by OVD. However, it would be difficult to explain as to how these OVDs transforms into OVCs which have minimal dysplasia.[3]

Our previous findings have demonstrated a high negative predictive value of VELscope examination of 95.08%, suggesting its potential as an adjunct to eliminate rather than to confirm the presence of malignant change during clinical examination.[12] This may prove to be advantageous to alleviate patient and practitioner anxiety about a clinically doubtful exophytic VPL in the background of OSF which may reduce patient reluctance for biopsy procedure.[12] We report FVI in EVH in OSF for the first time. This VELscope finding of increased fluorescence could be due to increased keratinization of the lesion or retained betel quid/bacterial plaque on the surface of the mucosa or yet unrecognized mechanism related to EVH. However, the use of VELscope in EVH needs to be substantiated with a larger sample size.

CONCLUSION

EVH in the background of OSF is a distinct entity from conventional OVC and OSCC. We highlight a particular group of OSF patients, who clinically presented as highly suspicious malignant verrucous growths which on VELscope examination exhibited increased autofluorescence and on histopathological examination revealed no signs of dysplasia or invasion. Exhibition of increased autofluorescence of these lesions on VELscope examination could greatly help to determine their nondysplastic nature.

Findings of our study led us to propose the new term OVD/EVD for lesions showing features of OVH/EVH with dysplasia while retaining the original term OVH/EVH for lesions without dysplasia. Further multicentric studies with large sample size are needed for the standardization

of clinical and histopathological criteria for EVH occurring in the background of OSF.

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Conflicts of interest

There are no conflicts of interest.

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