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Proliferative verrucous leukoplakia, an enigma to the pathologists: Report of two cases

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Abstract

The oral cavity presents with an array of white lesions ranging from physiological alteration to extensive malignant entities. Among them, proliferative verrucous leukoplakia is a rare highly aggressive multifocal form of leukoplakia that poses a high risk for malignant transformation. Etiopathogenesis and its diagnostic criteria have remained speculative since its inception. The diagnosis of this form of leukoplakia is challenging and it requires updated knowledge and expertise to identify this condition. All the cases of proliferative verrucous leukoplakia are resistant to treatment and have high chances of recurrence. In the present case report, we aim to report and document two cases of proliferative verrucous leukoplakia, which were diagnosed in a dental college. The present case report can serve as a guide to young dental surgeons to spot cases of proliferative verrucous leukoplakia and to refer them to tertiary care hospitals for treatment.

Keywords

Leukoplakia, malignant, proliferative, verrucous

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Introduction

White lesions are frequently encountered in the oral cavity. They may range from a clinically insignificant variation of the mucosa to highly significant malignancies. Proliferative verrucous leukoplakia (PVL) is a relatively rare multifocal lesion that poses a high risk for malignant transformation.[1] The first case of PVL was reported by Hansen et al.[1,2] However, the diagnosis of PVL has always been speculative since its discovery because of the lack of standard diagnostic criteria to define the entity precisely.[1,3] Many researchers have studied PVL, out of which the diagnostic criteria given by Cerero Lapiedra et al.[4] and Villa et al.[5] are followed worldwide for the diagnosis of PVL.

Despite advances in diagnostic and molecular pathology, the exact etiopathogenesis of PVL remains elusive. Pathologists consider it a multifactorial phenomenon.[3,6] In the initial years after its discovery, many authors considered that there is no association between tobacco smoking and the development of PVL.[4,7] This is because the early cases of PVL were identified in elderly females who were non-smokers and had never consumed alcohol. Alcohol and tobacco smoking are considered risk factors for leukoplakia but found to have no association with PVL. Recent literature reveals that PVL can develop in smokers also but its association with tobacco use remains unclear.[4,7,8] Candidiasis and human papillomavirus infection have been found in the cases of PVL; however, their exact role in the pathogenesis of PVL has not yet been defined.[8,9] The most commonly affected areas are buccal mucosa, gingiva, palate, and alveolar ridge but can involve the tongue and floor of the mouth as well.[1,6] The malignant transformation rates reported by Villa et al.[5] and Lafuente Ibanez de Mendoza I et al.[9] are 71% and 66%, respectively. The clinical presentation of PVL is identical to any other white lesions affecting the oral cavity. The uniqueness of this entity is in its widespread involvement in

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individuals with or without exposure to risk factors, and it has a progressive clinical course and a greater risk for malignant transformation.[1,3,6,9,10]

Two unique cases of PVL (one female and one male) are documented in this case report. The first case was seen in a middle-aged female with an extensive lesion on the left side of the oral mucosa and in the second case, the patient was a middle-aged male presenting a white lesion bilaterally on the buccal mucosa and gingiva. Both the patients were non-smokers. The present case report aims to discuss briefly the identifying features and treatment modalities of PVL, and to serve as a guide for general dental practitioners in the diagnosis and treatment/referral of PVL cases.

Case report 1

A 54-year-old female patient reported to the outpatient department of a dental college with a chief complaint of a progressing white lesion on the left side of the mouth for 2 years. The patient stated that it initially began as a pea-sized lesion and gradually progressed to the present state. The patient was a non-smoker; however, the patient gave a history of chewing areca nuts occasionally.

On examination, a diffuse, non-scrapable verruca-papillary lesion was noted on the entire mandibular buccal gingiva of the left side. The lesion extended to the mandibular left vestibular region and left buccal mucosa (Figure 1(a) and (b)). No other lesion was noted intraorally and extraorally. The mouth opening of the patient was normal. Correlating the clinical features, a provisional diagnosis of verrucous leukoplakia was given with the differential diagnosis, verrucous carcinoma, verrucous hyperplasia, and squamous cell carcinoma. An incisional biopsy was taken from the left buccal mucosa and was sent for histopathological examination.

The hematoxylin and eosin-stained section showed hyperplastic para keratinized stratified squamous epithelium with focal areas of parakeratin plugging and broad rete ridges. The epithelial cells showed mild pleomorphism, and the underlying connective tissue showed marked inflammation. The histopathological features were consistent with mild epithelial dysplasia (Figure 1(c)).

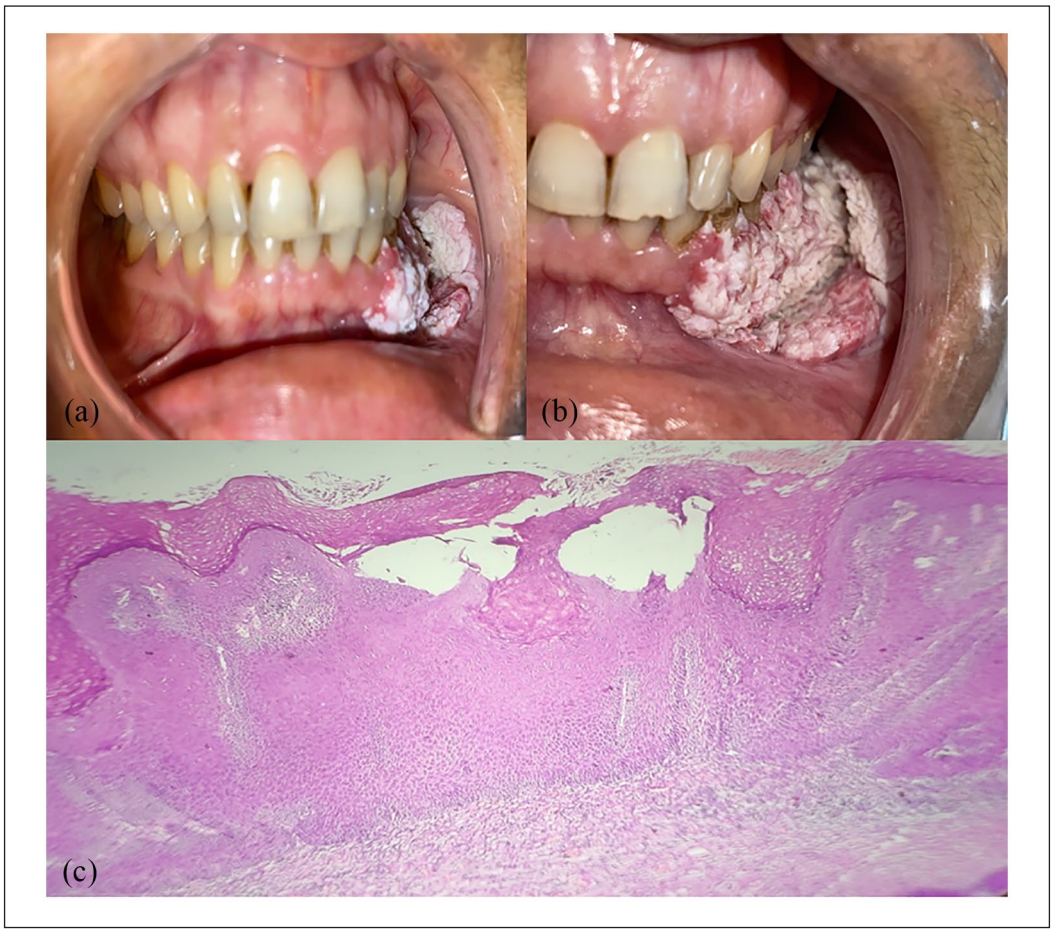

Figure 1. (a) and (b) A diffuse, non-scrapable verruca-papillary lesion was noted on the entire mandibular buccal gingiva of the left side. The lesion extended to the mandibular left vestibular region and left buccal mucosa. (c) Photomicrograph showing hyperkeratosis with mild epithelial dysplasia (100× magnification).

Table 1. Criteria to diagnose proliferative verrucous leukoplakia (Cerero-Lepiedra et al.[4]).

Major criteria (MC)	Minor criteria (mc)
A leukoplakia lesion with more than two different oral sites (A)	Leukoplakia lesion occupies at least 3 cm when adding all the affected areas (a)
Existence of a verrucous area (B)	The patient is female (b)
Lesions have spread or engrossed during the course of the disease (C)	Patient (male or female) is a non-smoker (c)
Recurrence in a previously treated area (D)	Disease evolution higher than 5 years (d)
Histopathology diagnosis (E)*	

*Histopathological diagnosis of the lesions that fall under the spectrum of proliferative verrucous leukoplakia (PVL) are hyperkeratosis, mild, moderate, severe dysplasia, verrucous hyperplasia, verrucous carcinoma, and squamous cell carcinoma.
**Any three major criteria or any two major criteria and two minor criteria which must include major criteria (E) is required for the diagnosis of PVL.

Table 2. Criteria to diagnose proliferative leukoplakia (Villa et al.[5])

Serial number	Criteria
1.	White/keratotic lesions that may be smooth, fissured, verrucous, or erythematous with or without ulcer.
2.	Multi-focal non-contiguous lesions OR a single large lesion >4.0 cm involving one site OR a single large lesion >3 cm involving contiguous sites.
3.	Lesions that progress/expand in size and/or develop multifocality over time.
4.	Histopathology, that if not overtly exhibiting dysplasia or carcinoma, shows hyperkeratosis, parakeratosis, atrophy, or acanthosis with minimal to no cytologic atypia (Keratosis of unknown significance), with or without a lymphocytic band, OR verrucous hyperplasia; these features must not support a diagnosis of frictional or reactive keratoses.

*All the criteria need to be fulfilled for the diagnosis of proliferative leukoplakia.

Correlating clinically and histopathologically, a diagnosis of PVL was given as per the criteria proposed by Cerero Lapiedra et al.[4] (Table 1) and Villa et al.[5] (Table 2).

According to Cerero Lapiedra et al.,[4] major criteria (A, B, C, and E), and minor criteria (ab) are being fulfilled to diagnose the case as PVL. All the criteria proposed by Villa et al.[5] were met for the diagnosis of proliferative leukoplakia (PL).

Case report 2

A 44-year-old male patient reported to the dental outpatient department with a chief complaint of painless white lesions in the entire mouth for 1 year which were initially small and gradually progressed to the present state. The patient gave a history of chewing areca nut occasionally for 15 years. On examination, non-scrapable gelatinous white lesions were noted on the right and left buccal mucosa and on the right mandibular marginal gingiva (buccal) around 44, 45, 46, and 47 teeth (Figure 2(a) and (b)). The mouth opening was normal and no fibrous bands could be palpated. Correlating the clinical features, a provisional diagnosis of multifocal leukoplakia was made.

An incisional biopsy was taken from the right and left buccal mucosa and was sent for histopathological examination. The findings of the biopsy reports from both sites were consistent with the diagnosis of hyperkeratosis with mild epithelial dysplasia (Figure 2(c) and (d)).

Correlating clinically and histopathologically, a diagnosis of PVL was given as per the criteria proposed by Cerero Lapiedra et al.[4] (Table 1) and Villa et al.[5] (Table 2).

According to Cerero Lapiedra et al.,[4] major criteria (A, C, and E), and minor criteria (a and c) are being fulfilled to diagnose the case as PVL. All the criteria proposed by Villa et al.[5] were met for the diagnosis of PL.

Discussion

Oral PVL was first described by Hansen et al.[2] Ever since its discovery, it has been an interesting, yet debatable topic for pathologists to discuss.[3,6] Different diagnostic criteria have been proposed, and a lot of discussions in various meetings went through regarding PVL.[11] The criteria proposed by Cerero Lapiedra et al.[4] (Table 1) were followed for the diagnosis of PVL, till 2018, when Villa et al.[5] proposed the term PL and simplified its diagnostic criteria (Table 2).[5] The reasons put forward by Villa et al.[5] for renaming the PVL group of lesions were not all the cases showed verrucous areas in their presentation. Villa et al. further emphasized that the progressiveness of the lesions should not be a mandatory criterion for the diagnosis of PVL. They stated that by the time the lesions are multifocal, they have progressed over time.[5] The initial presentation of PVL could depict flat, white areas or even be associated with a lichenoid appearance. In the latter group of lesions, it could be erroneously treated as per the treatment protocols of oral lichen planus, missing out on an impending or already progressed malignancy.[10] Although the term PVL is imperfect, and it becomes difficult to diagnose the condition, the World Health Organization Working Group (2022) still recommends retaining this term.[10]

Thompson and his colleagues from the United States in the year 2021 studied the different aspects of PVL. They

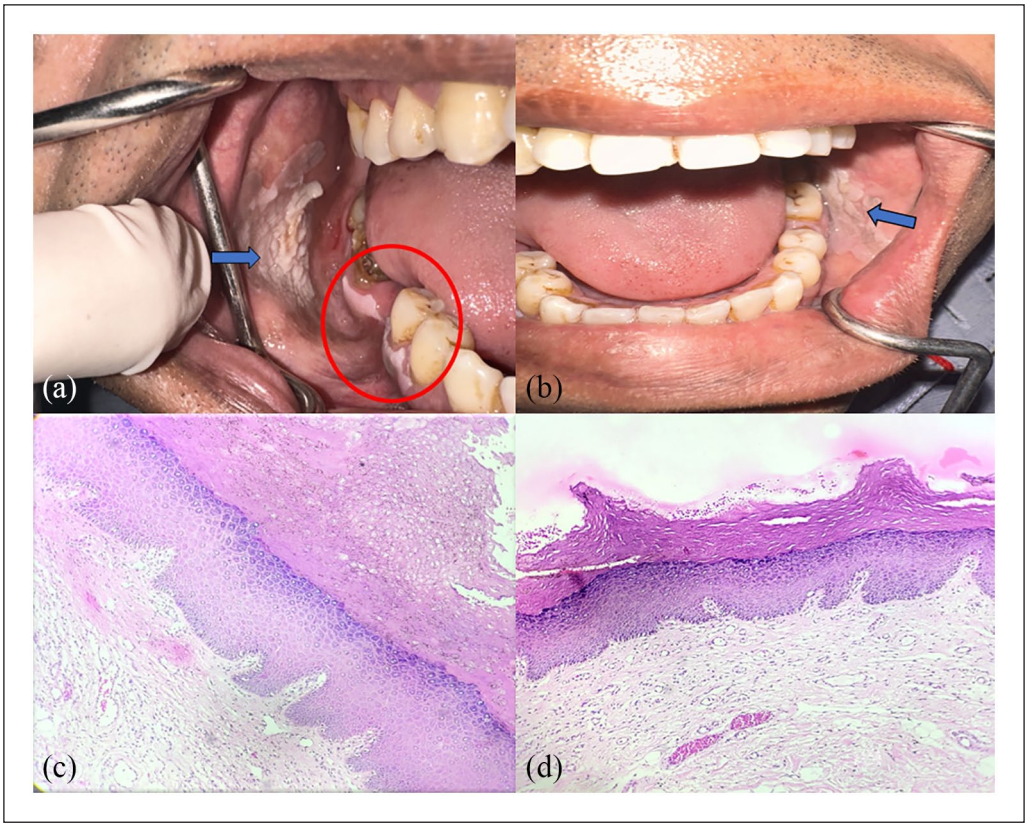

Figure 2. (a) Diffuse white patch on the right buccal mucosa (blue arrow), white patch noted on the gingiva around 44, 45, 46, and 47 teeth. (b) Diffuse gelatinous white patch on the left buccal mucosa (blue arrow). (c) Photomicrograph showing hyperkeratosis with epithelial dysplasia of the biopsy taken from right buccal mucosa (100× magnification). (d) Photomicrograph showing hyperkeratosis with mild epithelial dysplasia of the biopsy taken from left buccal mucosa (100× magnification).

subdivided the PVL group of lesions into three categories, namely corrugated ortho(para) hyperkeratotic lesions (non-reactive), bulky hyperkeratotic epithelial proliferation (non-reactive), and lesions that are suspicious for squamous cell carcinoma.[11] The authors studied different aspects of these groups of lesions and devised the histopathologic criteria for each group of lesions to be included in the spectrum of PVL.[11]

The etiopathogenesis of PVL has also been speculated since its discovery.[1,3] Okoturo et al.[12] in their systematic review highlighted different etiologies that could be attributed to the pathogenesis of PVL.[12] Viral infections which include human papillomavirus, Epstein-Barr virus, herpes simplex virus, polyomavirus, and fungal infections most frequently candida infections have been identified in the cases of PVL, although their exact role in the pathogenesis of PVL is yet to be determined.[3,9,12] p53 over-expression has been noted in cases of PVL when compared to oral squamous cell carcinoma; however, no studies reported mutation of tumor protein p53.[12,13]

Deoxyribonucleic acid (DNA) aneuploidy in PVL has been investigated; however, no concrete evidence has been found between DNA aneuploidy status and malignant transformation in PVL.[13] Pentenero et al.[13] mentioned that malignant transformation in PVL is more frequent in females and most commonly involves the masticatory mucosa.[13] Herreros-Pomares et al.[14] conducted a study on the tissue samples of already diagnosed cases of PVL to explore the molecular biology of PVL through methylated DNA immunoprecipitation and high-throughput sequencing and found that 4647 differentially methylated regions were found in cases of PVL, their integrated analysis revealed eight genes which were significantly upregulated and five genes which were significantly down-regulated in PVL cases when compared to healthy controls.[14] Okoturo et al.[15] in their study of whole-exome sequencing of 5-PVL-associated oral squamous cell carcinoma cases, noted that there were modified spectrum of PIK3CA and NOTCH1 mutations.[15]

Early detection and prompt treatment of PVL cases could minimize damage and improve the quality of life of the patients.[3] The treatment modalities for PVL include traditional surgery, cryosurgery, electrosurgery, laser surgery, administration of cytotoxic drugs, and photodynamic therapy (PDT).[16] Romeo et al.[16] treated a case of PVL in an elderly female with PDT, using 5-aminolevulinic acid (5-ALA). The authors followed up on the case for 12 months,

and no recurrence was reported.[15] The only drawback of PDT is it has limited depth of penetration and cannot be beneficial for deeper lesions.[16] Aash A and his colleagues in their case report presented a case of PVL treated with excision with a safe margin of 0.5 cm and the surgical defect was restored with the buccal pad of fat (BPF) harvested from the adjacent uninvolved area underlying the buccinator muscle. The reconstructed site was covered with platelet-rich plasma (PRF) membrane and covered by suturing with an additional layer of BPF.[17] The patient was followed up for 6 months, the healing was uneventful and no recurrence was reported.[17] Even though a substantial number of treatment strategies are available for PVL, there is no scientific evidence to draw an inference that any of them could reduce its recurrence rate.[3,5,16,17]

The cases presented in this case report were diagnosed based on the clinical and histopathological criteria given by Cerero Lapiedra et al.[4] and Villa et al.[5] The patients diagnosed with PVL should be closely followed-up and will need multiple sequential biopsies over the years. Since we do not have the facility for advanced surgical procedures in our hospital, the patients were referred to the super-specialty cancer hospital for treatment. Therefore, we could not comment on the progression or the treatment outcome (if any) because the patients have not reported back. We could not perform any immunohistochemistry (IHC) or molecular studies due to the lack of facilities in our country. Failure to give follow-up data and to perform molecular studies of the presented cases are the limitations of this case report.

Conclusion

PVL is a rare, highly aggressive multifocal form of leukoplakia with a high risk for malignant transformation. Research regarding its pathogenesis and biological and clinical behavior has been ongoing since its inception. Despite extensive research, much information, especially about epigenetic dysregulations in PVL, is yet unknown. In the present case report, we have described two cases of PVL and highlighted its clinical features, and diagnostic criteria, which can serve as a guide to young clinicians to diagnose the condition and refer the patients to higher centers for treatment and follow-up. We hope multicentric studies involving PVL will come up in the future, and unveil it further.

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Author contributions

S.G. Conceptualization, investigation, supervision, writing—original draft, writing—review and editing. S.D. Conceptualization, supervision, writing—review and editing. P.P. Conceptualization, writing—review and editing. S.A. Data curation, investigations, supervision, writing—review and editing.

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Ethics approval

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Informed consent

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