Proliferative Veruccous Leukoplakia: An Extensive Red and White Lesion

Arya S Nalin1, Radhakrishnan Jayakrishnan2, Sherin Ziaudeen3, M Ameena3, N J Naziya1
1Post Graduate Student, Department of Oral Medicine and Radiology, Mar Baselios Dental College, Kothamangalam, Ernakulam, Kerala, India, 2Assistant Professor, Department of Community Oncology, Regional Cancer Centre, Thiruvananthapuram, Kerala, India, 3Post Graduate Student, Department of Oral and Maxillofacial Pathology, Azeezia College of Dental Science and Research Centre, Meeyannoor, Kerala, India

Proliferative verrucous leukoplakia (PVL) is a rare form of leukoplakia, which was first described by Hansen et al. in the year 1985. PVL is a disease with aggressive behavior due to its high rate of recurrence and a high rate of malignant transformation, usually more than 70%. This is a long-term progressive condition, which is observed more frequently in females over the age of 60 years. In the course of time, PVL tends to become multifocal with progressive deterioration of the lesions, making it more and more difficult to control. Unlike other cases of leukoplakia, tobacco use does not seem to have a significant influence on the appearance and progression of PVL. As this condition is seen in non-smokers, the etiology of PVL remains unclear making the management and diagnosis difficult. The aim of this article is to present a case which is diagnosed based on the diagnostic criteria proposed by Cerero-Lapiadra et al.

Keywords: Carcinoma, Hyperkeratosis, Leukoplakia, Verrucous leukoplakia

INTRODUCTION

The prevalence of white lesions either due to physiologic or pathologic process in the oral cavity is approximately 24.8%.1 Among them is oral leukoplakia is reported to have an estimated world leukoplakia prevalence of 2% by Petti,2 while a rate of 0.5% or lower as reported by van der Waal.3 According to World Health Organization Leukoplakia was described as a “premalignant lesion.”4 However, recently suggestions are made to substitute the terms “premalignant” and “premalignant” by “potentially malignant,” and that all premalignant lesions and conditions should be grouped under the common entity of “potentially malignant disorders.”5 The latest Workshop on oral precancer organized by World Health Organization in collaboration with Centre for Oral Cancer in 2005, oral leukoplakia should be defined as “a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer.”3,5 Despite these modifications in its nomenclature and classification, oral leukoplakia remains the most frequent potentially malignant disorder in the oral cavity with its malignant transformation rate varies from 0.13% to 17.5%.6

A rare form of oral leukoplakia known as proliferative verrucous leukoplakia (PVL) was first reported barely a few decades ago by Hansen et al. It has a more aggressive biological behavior than other forms of leukoplakia as it has a tendency toward multifocality; a high probability of recurrence; and a high rate of malignant transformation, between 40 and 100% in a period of about 4.4-11.6 years.7,8 In 1985 Hansen described PVL as a long-term progressive condition which develops initially as a white plaque of hyperkeratosis that eventually becomes a multifocal disease with confluent, exophytic, and proliferative features.

As per literature, PVL seems to have an increased predilection for non-smoking elderly female patients over the age of 60 years without any racial predilection unlike other cases of leukoplakia, which is prevalent in smoking males.9,10 Tobacco does not seem to have a significant influence on the disease as PVL occurs both in smokers and non-smokers especially non-smokers.11 These lesions usually present as slow-growing yet persistent, as well as irreversible and resistant to all forms of treatment with a high recurrence rate. During development, it is common to find erythematous and or verrucous areas that occasionally progress to verrucous carcinoma or squamous cell carcinoma (SCC).
Recently, our department attended a patient with PVL that developed extremely rapidly, with only 12 months from the appearance of white patches to their cancerous transformation. Consequently, this case warrants attention. We describe this case with reference to the relevant literature.

**CASE REPORT**

A 66-year-old female patient presented with a chief complaint of burning sensation of the tongue and palate since 1 year. A small white ulcerated patch first appeared on the roof of the mouth. This patch apparently grew to cover the entire palate and anterior gingiva over the course of a year. A mild localized burning sensation was experienced which was of gradual onset. No parasthesia or neurosensorial disturbances were reported. The medical history elicited revealed no comorbid conditions or any immune-related disorders. The patient had been a betel quid user for the last 40 years, and used to chew 4-5 times/day, but has ceased since two months due to burning sensation.

On intraoral examination, the mucosa of the hard palate showed a white nodular patch measuring 6 cm × 4 cm in size, with interspersed erythematous areas, having irregular borders (Figure 1). Anteroposteriorly, it extended from the anterior alveolar margin to the junction of hard and soft palate, and mesiolaterally from the right alveolar margins across the midline to the left alveolar margins. The anterior two-third of the lesion had a moist, velvety granular appearance whereas, at the posterior one-third, the lesion appeared to have white granular velvety areas intermixed with erythematous areas. The lesion finally covered the maxillary alveolar ridge from the distal end of first premolar to the mesial end of the second molar region as a thick homogenous white plaque. The lesion was also seen on the attached gingiva from distal of 13 to distal of 23 (Figure 2). On palpation, the lesion was tender in the region of the labial and buccal mucosa. The texture was rough and leathery with some areas of induration.

Based on the clinical presentation and the involvement of multiple sites we put forward a provisional diagnosis of PVL. As differential diagnosis, we also considered chronic hyperplastic candidiasis, SCC, and verrucous carcinoma.

As the lesion extended over the hard palate, an occlusal radiograph was taken which ruled out any bony involvement. The biopsy was taken from the posterior part of the hard palate and was sent for histopathological examination; which showed severe dysplasia (Figure 3).

Based on clinical features, histopathological diagnosis as well as the Cerero–Lapiedra classification for PVL, we confirmed our provisional diagnosis of PVL.

**DISCUSSION**

The term PVL was introduced in the year 1985 by Hansen who defined it as a disease of unknown origin that clinically often begins as a single white lesion and along
with time tends to become multifocal, growing slowly and progressively. Unlike conventional leukoplakia, it is seen to occur predominantly in women of middle age and they constitute 72% of the affected population. In our case, the patient was a female past her middle age.

This lesion can arise in any site within the oral cavity and shows a marked risk of progressive transformation from PVL to verrucous hyperplasia and finally to verrucous carcinoma. The risk of such transformation may be as high as 64% and the risk of recurrence about 88%. Studies by Bagan et al., Hansen et al. and Silverman and Grosky have estimated the duration for malignant transformation to range between 4.7 and 11.6 years but our case showed a much more accelerated growth rate as the lesion spread within a short span of just 1-year.

Though the exact etiology is unknown, immune factors and infectious agents have been implicated as causative factors. As the immune system plays a crucial role in the prevention of malignant transformation by way of immune surveillance, any defect or impairment in this mechanism can lead to the emergence of conditions like PVL. An alternate hypothesis suggests that since PVL exhibits the phenomenon of “field cancerization” an infectious agent could be considered as a possible etiology. The most likely of those considered are human papillomavirus (HPV) strains 16 and 18 as well as Epstein-Barr virus.


Hansen et al. classified the pathological process of PVL into 10 grades: Normal oral mucosa (0), homogeneous leukoplakia (2), verrucous hyperplasia (4), verrucous carcinoma (6), papillary SCC (8) and poorly differentiated carcinoma (10). The odd scores refer to a status intermediate between those referred to by the adjacent even scores.

An important contribution was made by Cerero-Lapiedra et al. when they evolved a diagnostic criterion for the identification of PVL (Table 1) that we employed in our case. Our case satisfies three major criteria and two minor criteria.

The treatment modalities of PVL are varied. Laser therapy using carbon dioxide (CO₂) laser was reported to be successful in a small group of 70 patients but further studies are needed to confirm its effectiveness. Chemotherapy has also been done with several drugs including topical bleomycin solution, oral retinoids, beta carotene and methisoprenol. Methisoprenol is used in cases where HPV is considered as the etiologic factor. Surgical removal of the lesion has been done in some cases and in other cases photodynamic therapy has also been used. Photodynamic therapy is considered to be advantageous because of its slow morbidity, non-scarring and the ability to treat multiple sites at once. A combination of the aforementioned modalities has also been used in an attempt to improve the outcome but as the lesion has a very high rate of recurrence it shows an overall poor response to treatment.

CONCLUSION

PVL is a lesion that needs to be approached with more caution than your average white lesion. In order to arrive at a correct diagnosis of PVL it is essential that both the clinical features and the histopathological appearance be correlated. It is imperative to provide the pathologist with biopsies from multiple sites, the age and sex predilection and a clear clinical picture of the lesion.

REFERENCES


Table 1: Diagnostic criteria for pvl

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tbody>
<tr>
<td>A leukoplakia lesion with more than two different oral sites, which is most frequently found in the gingiva, alveolar processes and palate</td>
<td>An oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas</td>
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<td>The existence of a verrucous area</td>
<td>That the patient be female</td>
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<td>That the lesions have spread or engrossed during the development of the disease</td>
<td>That the patient (male or female) be a non-smoker</td>
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<td>That there has been recurrence in a previously treated area</td>
<td>A disease evolution higher than 5 years</td>
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<td>Histopathologically, they can be from simple epithelial hyperkeratosis to verrucous hyperplasia, verrucous carcinoma or squamous cell carcinoma</td>
<td>Whether in situ or infiltrating</td>
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