Review Article

Proliferative verrucous leukoplakia: A diagnostic dilemma

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ABSTRACT

Oral leukoplakia is one of the most common potentially malignant disorders of the oral cavity. Many variants of oral leukoplakia exist, with oral proliferative verrucous leukoplakia (OPVL) being one. OPVL, a slow growing, long-term progressive lesion was first described in 1985 by Hansen *et al*. It is an aggressive form of oral leukoplakia with multifocal presentation, high rates of malignant transformation and recurrence. It is a rare clinico-pathological entity, which remains an enigma even today. The term proliferative verrucous leukoplakia (PVL) has been the subject of an ongoing discussion with regard to its definition. Its etiology too remains unclear until date. Tobacco use does not seem to have a significant influence on the appearance or progression of PVL. These lesions are known to occur in both smokers and nonsmokers. In the light of current information available, this article describes the etiology, clinical aspects, histological features, and various diagnostic criteria of OPVL.

Key words: Hyperkeratosis, oral leukoplakia, oral proliferative leukoplakia, potentially malignant disorder

INTRODUCTION

Oral cancer is among the ten most common cancers worldwide, with a wide geographical variation in its incidence.[1] The cause of oral squamous cell carcinoma (OSCC) is multifactorial. Many OSCCs seem to be associated with or preceded by premalignant lesions, especially leukoplakia. Leukoplakia is defined as "a white plaque of questionable risk, having excluded (other) known diseases or disorders that carry no increased risk for cancer."[2] Leukoplakia was described by the World Health Organization as a "precancerous lesion." However, more recently it has been suggested that the terms "premalignant" and "precancerous" should be substituted for "potentially malignant," and that all precancerous lesions and conditions should be grouped under the common name of "potentially malignant disorders."[3] Proliferative verrucous leukoplakia (PVL) was first described by Hansen *et al*. in 1985[4] as a long-term progressive condition, which develops initially as a white plaque of hyperkeratosis that eventually becomes a multifocal disease. As there are no particular differences between the pathological changes of PVL and those of oral verrucous leukoplakia (OVL), the characteristics of its clinical and pathological progress are considered vital bases for the diagnosis of PVL.[5] The premalignant capacity of PVL is higher than the one observed in "common leukoplakia." Therefore, the early diagnosis of this pathology plays a crucial role when trying to prevent a malignant transformation in PVL or at least when trying to prevent the development of carcinomas.

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ETIOPATHOGENESIS

Oral proliferative verrucous leukoplakia (OPVL) is a rare clinico-pathological entity, which remains an enigma even today. Also factors responsible for its development are unclear. Tobacco use does not seem to have a significant influence on the disease because PVL occurs both in smokers as well as in nonsmokers.[6] However, cases reported in the literature seem to implicate immune factors. Enhancing the patient's immunity and topical therapies are known to have a positive effect. There are some reported cases of patients with PVL after bone-marrow transplantation (BMT) supporting this impression.[7] BMT involves an immunosuppressive step, and oral squamous cell carcinoma (OSCC) is a malignancy that can occur after BMT.[8] This indicates that immunity plays a significant

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role in PVL, as in OSCC. Also, epidemiological data have demonstrated a high incidence of PVL in elderly women, with no history of tobacco or alcohol consumption. This could be attributed to lower immunity in women as compared to men and also decreased immunity with age.[8] Some authors have also reported an association between human papillomavirus (HPV) and PVL[9] particularly HPV16 and HPV18. Historically, it has been postulated that HPV infection begins with the inoculation of virus into an interruption of epithelium and the interaction with a putative specific cellular receptor. The early viral gene products stimulate cell growth in the basal layer, leading to epithelial proliferation and formation of an exophytic lesion.[10] Between 0% and 89% OPVL are reported to be HPV-positive.[11] However, HPV were found in only a small number of cases, and other authors have been unable to find any such association. For example, Campisi *et al*. using nested polymerase chain reaction (PCR) – a sensitive technique-studied 58 cases of PVL compared with 90 cases of other oral leukoplakias and concluded that PVL is not more likely to be associated with HPV infection than is conventional leukoplakia. Using PCR, we also could not find an association.[12] Jose Bagan *et al*. in their study detected Epstein-Barr virus (EBV) in PVL and also in a higher percentage of patients with PVL associated OSCC as compared to OSCC without PVL. However, they did not find any evidence of any direct role of this virus in the etiology.[12] PVL patients infected with HPV or EBV might be immunocompromised like human immunodeficiency virus-infected patients.[8] Silverman *et al*. reported 68% of PVL patients to be positive for *Candida albicans* but did not find the fungal infection to be linked to PVL occurrence or it is progression to carcinoma.[13] Recently, it has been shown that frequent alterations of cell cycle regulatory genes, p16INK4a and p14ARF, are common in OVL.[13] LOH was the most frequent molecular alteration detected in the PVL lesions. Allelic loss at 9p21 was detected in at least one microsatellite marker in 63.2% of PVL patients.[13] In addition to that, transforming growth factors-alfa expression, deoxyribonucleic acid ploidy, up-regulation of cyclooxygenase-2 and p53 mutation have been studied in PVL.[11]

CLINICAL FEATURES

Proliferative verrucous leukoplakia is a rare and specific disease that differs from OVL and is commonly seen in middle-aged and elderly women in the ratio of 4:1. It has been shown that almost all the lesions occur bilaterally, predominantly on the buccal mucosa followed by the palate, gingiva, and tongue. It represents a simple benign form which tends to spread and becomes diffuse.[13] Then it further progresses with different forms of presentation (homogeneous, patchy, verrucous) which in turn progress towards OSCC in over 70% of cases – with the successive appearance of multiple primary tumors (a phenomenon known as "field cancerization")[14] [Figure 1]. PVL is usually chronic and progressive, and a patient has a long history of leukoplakia before he or she attends a clinic.[15]

HISTOLOGY

Histologically, the early lesions are deceptively bland, showing only hyperkeratosis, but over time they become progressively verrucous and often show varying degrees of epithelial dysplasia [Figure 2].[8] There is an abrupt transition from hyperparakeratosis to hyperorthokeratosis, associated with a corrugated or verruciform surface.[16,6] Hansen *et al*. classified the pathological process of PVL into 10 grades, that is, normal oral mucosa (0), homogeneous leukoplakia (2), verrucous hyperplasia (4), verrucous carcinoma (6), papillary squamous cell carcinoma (8), and poorly differentiated carcinoma (10), in which the odd scores refer to a status intermediate between those referred to by the adjacent even scores.[8]

Batsakis *et al*. reduced the number of histologic stages to four with intermediates:

- Grade 0: Clinical flat leukoplakia without dysplasia
- Grade 2: Verrucous hyperplasia
- Grade 4: Verrucous carcinoma
- Grade 6: Conventional squamous cell carcinoma with intermediates.

In early phases, it shows lymphocytic infiltrate along with pronounced lichenoid pattern characterized by basal vacuolar degeneration containing apoptotic cells and eosinophilic bodies, similar to lichen planus.[11] Therefore, PVL has no characteristic histopathological features.

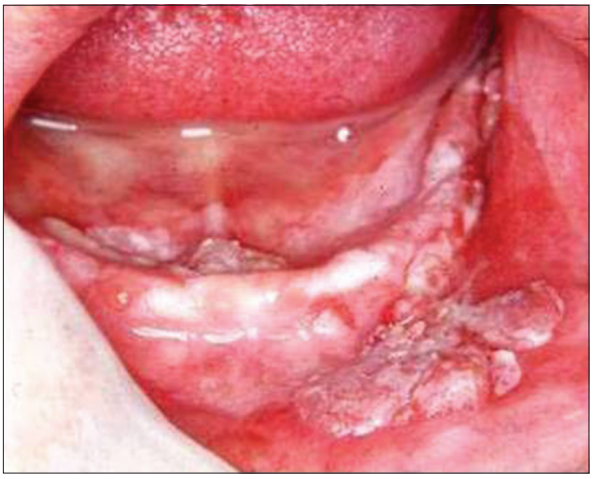

Figure 1: Coexistence of lesions at various stages of evolution in the same proliferative verrucous leukoplakia case

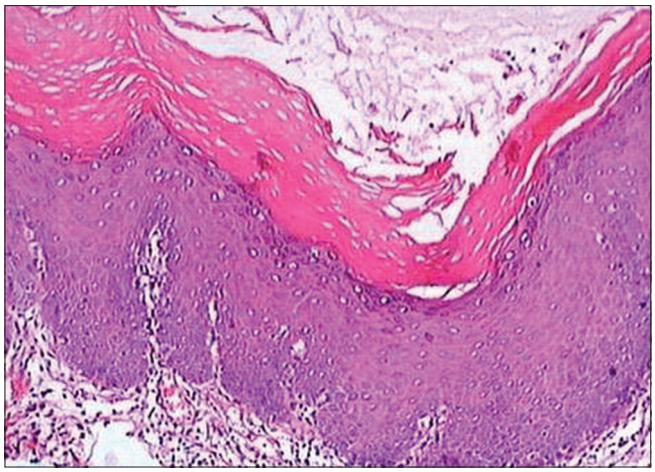

Figure 2: The right buccalverrucous leukoplakia with mild to moderate dysplasia (×100)

DIAGNOSIS

Diagnosis of PVL is according to Hansen's first definition in 1985, not taking into account the latter ones. There are two previous studies, one by Ghazali *et al.* and another by Gandolfo *et al*., which tried to develop a set of diagnostic criteria to their respective cases, although these are just a transcription of Hansen's definition.[17]

Ghazali *et al.* established the following criteria

- The lesion starts as homogenous leukoplakia without evidence of dysplasia at the first visit
- With time, some areas of leukoplakia become verrucous
- The disease progresses to the development of multiple isolated or confluent lesions at the same or a different site
- With time, the disease progresses through the different histopathological stages reported by Hansen *et al*
- The appearance of new lesions after treatment
- A follow-up period of no <1-year.

Gandolfo *et al*., establish the following criteria

- An initially innocuous lesion characterized by a homogenous plaque that progresses over time to an exophytic, diffuse, usually multifocal, lesion with a verrucous epithelial growth pattern
- Histopathologically, PVL changes gradually from a simple plaque of hyperkeratosis without dysplasia to verrucous hyperplasia, verrucous carcinoma or OSCC.

Cerero-Lapiedra *et al.* proposed diagnostic criteria for PVL using a set of major and minor criteria

Major criteria

- A leukoplakia lesion with more than two different oral sites, usually gingiva, alveolar ridge, and palate
- Presence of a verrucous area
- The lesions have spread or engrossed during the development of the disease
- There has been a recurrence in a previously treated area
- Histopathologically, we can find from simple epithelial hyperkeratosis to verrucous hyperplasia, verrucous carcinoma or squamous cell carcinoma, *in situ* or infiltrating.

Minor criteria

- An oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas
- The patient is a woman
- The patient (male or female) does not smoke
- Disease evolution longer than 5 years.

In order to establish the diagnosis of PVL, it was suggested that two of the following combinations have to exist: Three major criteria (E being among them) or two major criteria (E being among them) plus two minor criteria.[18]

MALIGNANT RATE AND RECCURENCE

The issue that is central and which needs to be unraveled is its clandestine pathogenesis, as nearly 60–70% of PVL patients develop either a verrucous carcinoma or squamous cell carcinoma in contrast to conventional oral leukoplakia where the rate of malignant transformation is much lesser.[13] PVL grows slowly. The process is irreversible and usually progresses to cancer. According to the study by Bagan *et al*., PVL quickly becomes malignant, on average within 4.7 years[19] whereas, Hansen *et al*. reported an average time to cancer of 6.1 years. However, Silverman and Gorsky reported a longer mean malignant process of 11.6 years.[13] PVL is a clinicopathologic disease with high potential for malignant transformation whose diagnosis is retrospective. According to Silverman and Gorsky (1997),[13] 70.3% of the patients studied, developed a squamous cell carcinoma at a PVL site, over a mean time of 7.7 years. Thus, PVL must be considered an aggressive lesion.[20] The appearance of mild erythematous discoloration and granular texture, which suggests epithelial erosion proved to be more effective indicators of malignancy than indurated or nodular aspects.[21] PVL shows almost 100% rate of malignant transformation, mainly over an extended follow-up period. On the other hand, it is accepted that approximately 5% of all non-PVL leukoplakias will become cancer over an average period of 5 years.[22] PVL is resistant to the available treatment modalities, such as cold knife surgery, CO_2 laser evaporation, laser surgery, radiotherapy, chemotherapy and presents frequent recurrences.[8] The mean age of diagnosis of carcinoma associated with PVL, being slightly over 60 years, may be explained by the accumulation of somatic mutation associated with the emergence of

malignancies.[13,23] Another feature of inherited precancerous condition that may be fitting to PVL pathogenesis is that it may be caused by defects in DNA repair gene, resulting in DNA instability.

CONCLUSION

Proliferative verrucous leukoplakia is known for its aggressive nature and tendency to recur after its removal. Thus, special awareness on the part of the clinician is extremely important. Therefore, it is recommended to have the earliest possible diagnosis, as well as consensus on diagnostic criteria to achieve uniformity. The follow-up of patients for a long time even after surgical management is of utmost importance.

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