Review Article

Proliferative Verrucous Leukoplakia – A Recalcitrant

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Abstract:
A rare, recalcitrant, and lethal form of leukoplakia necessitate special attention. The purpose of this review is to further educate and to characterize the risk factors, clinical course, and optimal treatment for this highly aggressive, premalignant oral lesion. White lesions are relatively frequent in the oral cavity with prevalence of approximately 24.8%. Among them oral leukoplakia (OL) is quite prevalent (0.2-3.6%). Hansen et al in a retrospective study reported that 26 of the 30 lesions initially diagnosed as OL became oral carcinomas in patients followed for 1-20 years (average, 6.1 years). After this study, these lesions were named oral proliferative verrucous leukoplakia (OPVL). World Health Organization nomenclature, OPVL conforms to the new terminology of "potentially malignant disorders" given that it is neither a delimited lesion nor a condition.
Key words: Oral proliferative verrucous Leukoplakia (OPVL), White Lesion, Leukoplakia

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INTRODUCTION

The term leukoplakia was first used by Schwimmer in 1877 to describe a white lesion of the tongue, which probably represented a syphilitic glossitis.[1] Type of leukoplakia, OPVL was first described by Hansen. It is 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 and behaves in a more aggressive and relentless manner than the more innocuous white oral lesions that it can resemble clinically. It is a special high risk form of leukoplakia. The difficulty in the early diagnosis stems from the overlapping clinical and pathologic features with conventional multifocal leukoplakia with dysplasia of PVL. The aetiology of the process remains unclear, and the treatments used (analogous to those usually employed in the management of leukoplakia) appear to be scantly effective in controlling the disease – though few studies on the treatment of PVL can be found in the literature.[2]

ETIOPATHOGENESIS:

The exact etiologic agent of PVL is still not known. Patients usually have a history of minimal tobacco exposure, 37% in a review of 137 patients by Cabay et al. The frequent absence of risk factors, a preponderance of women patients and occurrence at an older age suggests that the pathogenesis of carcinoma arising in

PVL may be different from that of non PVL associated carcinoma. 89% positivity for HPV DNA using PCR was found by Palefsky. However, studies by Fettig et al have shown that no HPV was detected in the ten gingival PVL cases that he studied. Studies by Bagan et al detected EBV in a higher percentage of patients with PVL when compared with Oral Squamous cell carcinoma without PVL although the role of EBV as an etiologic agent could not be proved.[5] For the first time it has been shown that frequent alteration of cell cycle regulatory genes, p16INK4a and p14ARF is common in oral verrucous leukoplakia. These changes thus illustrate that molecular alterations are associated with distinct histologic types of oral premalignancy, which may affect disease progression, treatment strategies, and ultimately PVL.[11]

PVL has a strong female predilection (1:4 male to female). The gingiva and tongue are the most common sites of transformation observed in PVL. Initially it appears as a white plaque of hyperkeratosis that eventually becomes a multifocal disease with confluent, exophytic and proliferative features. The lesions are slow- growing yet persistent, as well as irreversible and resistant to all forms of treatment with a high recurrence rate.[9]

HISTOPATHOLOGICAL FEATURES

PVL exhibits progressive histopathological features that may be observed in a single biopsy, multiple biopsies taken from a single patient at the same time or serial biopsies taken over time. If the lesions continue to grow horizontally and vertically, there are concurrent histopathological features of increasing hyperkeratosis with increased surface folding, verrucous papillomatosis, acanthosis and basilar hyperplasia with or without dysplasia. It is of interest that the early phase of these lesions usually exhibits a lymphocytic infiltrate at the interface that may have a pronounced lichenoid pattern characterized by basal vacuolar degeneration containing apoptotic cells and eosinophilic bodies, similar to types of oral lichenoid stomatitis such as lichen planus.[12] From the histological perspective, it is thus suggested that a stage of PVL must be considered in a lesion with features of lichenoid inflammation with basilar hyperplasia. The inflammatory component, although nonspecific from the histologic standpoint, has a telling effect on cancer development. This association has been demonstrated in the setting of unresolved chronic inflammation of viral hepatitis, owing to maladaptive immune response thereby promoting tumorigenesis.[8] It has also been suggested that chronic inflammation may increase the pool of tissue stem cells which may become subjected to the effect of mutagens. Only if these latter histopathological changes are observed and or there is a recurrence of a previously excised lesion could a white lesion be considered consistent with PVL clinically as stated by Cabay et al. The precise classification of PVL in a staging continuum is problematic because sampling of the lesions occurs at uncontrolled intervals and because of the minimum cellular atypia often seen on biopsy.[13] Hansen *et al* proposed a microscopic grading of PVL on a scale from 0-10 denoting a continuum of severity that included histologically normal oral mucosa, clinically homogenous leukoplakia, verrucous hyperplasia, verrucous carcinoma, papillary squamous cell carcinoma, less differentiated squamous cell carcinoma and intermediates.[6] Batsakis et al suggested a histological staging of PVL that included 4 phases (clinically flat leukoplakia without dysplasia, verrrucous hyperplasia, verrucous carcinoma and conventional squamous cell carcinoma with intermediates. Since dysplasia is

absent or is a late feature in many cases, it may lead to less aggressive treatment early in the disease process. Further there is an overlap between verrucous hyperplasia and verrucous carcinoma in histologic evaluation. [7]For this reason, Murrah and Batsakis suggest that biopsies should be taken from the margins of the lesions. PVL being an clinical diagnosis, exact nature of the lesion can only be judged by its histopathological evaluation. Hansen et al. suggested histologic stages in the continuum of PVL.

Grade 0: normal mucosa
Grade 2: Hyperkeratosis (Clinical leukoplakia)
Grade 4: Verrucous hyperplasia
Grade 6: Verrucous carcinoma
Grade 8: Papillary squamous cell carcinoma
Grade 10: Less well differentiated squamous cell carcinoma

Batsakis et al. reduced the number of histologic stages to 4 with intermediates:
Grade 0: Clinical flat leukoplakia without dysplasia
Grade 2: Verrucous hyperplasia
Grade 4: Verrucous carcinoma
Grade 6: Conventional squamous cell carcinoma with intermediate

Proposal of Major and Minor Diagnostic Criteria for PVL recommended by Cerero-Lapiedra et al. (2010)[2]

Major Criteria (MC)

a) A leukoplakia lesion with more than two different oral sites, which is most frequently found in the gingiva, alveolar processes and palate
b) The existence of a verrucous area.
c) That the lesions have spread or engrossed during development of the disease.
d) That there has been a recurrence in a previously treated area
e) Histopathologically, there can be from simple epithelial hyperkeratosis to verrucous hyperplasia, verrucous carcinoma or oral squamous cell carcinoma, whether in situ or infiltrating

MINOR CRITERIA (mc)

A) An oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas.
B) That the patient be female
C) That the patient (male/female) be a non smoker
D) A disease evolution higher than 5 years

Nevertheless, at present, there is no criterion that will allow for the early diagnosis of the disease[13] Critical appraisal for diagnostic criteria given by Cerero-Lapiedra et al. (2010) was Modified by Vinicius C. Carrard et al (2013)

1. Leukoplakia showing the presence of verrucous or wartlike areas, involving more than two oral subsites. The following oral subsites are recognized: dorsum of the tongue (unilateral or bilateral), border of the tongue, cheek mucosa, alveolar mucosa or gingiva upper jaw, alveolar mucosa or gingiva lower jaw, hard and soft palate, floor of the mouth, upper lip and lower lip.
2. When adding all involved sites the minimum seize should be at least three centimetres
3. A well documented period of disease evolution of at least five years, being characterized by spreading and enlarging and the occurrence of one or more recurrences in a previously treated area.
4. The availability of at least one biopsy in order to rule out the presence of a verrucous carcinoma or squamous cell carcinoma.

EVOLUTION

Proliferative verrucous leukoplakia is characterized not only by a high rate of recurrences after treatment but also by malignant transformation in nearly 74% of

cases, with a tendency for several oral cancers to appear (Cabay et al, 2007). Hansen et al (1985) reported that thirteen out of 30 cases died from the disease, 14 were alive with PLV lesions, and three were alive without signs of PVL. Saito et al (1999) studied and compared the wide-spread oral leukoplakias and the localized ones. They found that the widespread multiple oral leukoplakias have a higher potential for the development of cancer than the localized lesions. Most of the multiple oral leukoplakias probably are Proliferative verrucous leukoplakias. Silverman and Gorsky (1997) presented the clinical course and outcomes in 54 cases, some of whom were from the initial series published by Hansen et al, 1985; and 21 of the patients died from oral squamous cell carcinomas. Zakrzewska et al (1996) presented 10 cases of PVL at first biopsy, no lesion was more serious than verrucous hyperplasia but eventually all developed oral squamous cell carcinomas. J Bagan *et al* ,2010 studied 30 patients with PVL for the clinical aspects and characteristics focusing on their recurrences, the appearance of new lesions, and the frequency of development of oral cancer. It was found that recurrences after treatment in 86.7% of cases, new lesions during follow up in 83.3%, and oral cancer eventually in 63.3%, with a high incidence on the gingivae.

TREATMENT:

Owing to the progressive nature of proliferative verrucous leukoplakia (PVL), many forms of therapy used for the management of traditional leukoplakia have been disappointing. Carbon dioxide laser, radiation, topical bleomycin solution, oral retinoids, beta-carotene, and systemic chemotherapy have all failed at achieving permanent cure. Although improvements have been noted with some of these modalities, recurrence rates after cessation of therapy are high, often within months of discontinuation of treatment.[4]

CONCLUSION:

Currently, most of the patients diagnosed with PVL end up being subject to multiple biopsies until finally being diagnosed with squamous cell carcinoma. By then it is often too late. Currently, poor outcomes with a high risk of progression to cancer may be reflective of undertreatment and lack of effective therapies for PVL. Thus, improving the prognosis in these patients will not only need improved diagnostic and therapeutic approaches but also greater collaboration between surgeon and pathologist. In fact, PVL is resistant to all the presently available treatment modalities and recurs frequently.[14] Thus Fettig et al. suggested aggressive surgery such as block resection. But total excision is rarely possible because of the widespread disposition of the lesion in the oral cavity. The challenge is to administer sufficiently aggressive therapy consistent with clinical progression of the lesion despite often benign histological findings.

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