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## Review Article

## บทความปริทัศน์

# Proliferative verrucous leukoplakia: a literature review

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### Abstract

This article presents proliferative verrucous leukoplakia (PVL), a distinct form of oral leukoplakia which exhibits aggressive behavior due to its high rates of recurrence and malignant transformation. It is a disease of unknown origin. The prevalence and distribution of this lesion are different from those of other forms of oral leukoplakia, and its clinical-pathologic appearance is varied, depending on the stage of development of the lesion. PVL is resistant to most kinds of therapy; therefore, the control of this disease is difficult, especially in the late course of disease in which multiple lesions usually occur. The early diagnosis of this lesion is necessary. Thus, the clinicians should recognize and be familiar with the expression of this disease.

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**Key words:** oral leukoplakia; proliferative verrucous leukoplakia; PVL

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### Introduction

The designation of leukoplakia is by far one of the most controversial definitions in the medical literature.<sup>1</sup> It was widely discussed and reclassified both formally and informally among epidemiologists, clinicians and pathologists from all over the world.<sup>2-6</sup> Oral leukoplakias are of particular importance because a significant number of them can transform into verrucous or squamous cell carcinoma.

There is one form of oral leukoplakia, called proliferative verrucous leukoplakia (PVL), which represents itself as a persistent, diffuse and multifocal white lesion with high recurrence rate.<sup>7</sup> PVL is a distinct clinical-pathologic entity of unknown origin which can present with a wide range of clinical appearance and microscopic findings, depending on the stage of development of the lesion.<sup>7,8</sup> The rate of malignant transformation of PVL is exceptionally high,<sup>7,9</sup> and

about half of patients die of PVL-associated carcinomas.<sup>9</sup> The diagnosis can only be made retrospectively.<sup>1,7,8</sup> Therefore, it is essential for clinicians and pathologists to recognize this disease and understand its natural behavior, in order to properly diagnose, manage the patients and be aware of its aggressive potential.

### **Oral leukoplakia: the general description and its importance**

In 1978, the WHO Collaborating Centre for Oral Precancerous Lesions defined the term “leukoplakia” as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease.<sup>2</sup> Therefore, leukoplakia is a negatively defined entity, diagnosed by exclusion of other common mucosal diseases, such as lichen planus, frictional keratosis, morsicatio, candidiasis, leukoedema and others.

This definition was revised in the international seminar in oral leukoplakia and associated lesions related to tobacco habits held in 1983, and it was emphasized that the term leukoplakia should be omitted if any physical or chemical causative agents can be identified, except the use of tobacco.<sup>3</sup> However, the tobacco-associated lesion labeled nicotine stomatitis or smoker’s palate is still listed separately from leukoplakia because of its typical characteristics.<sup>3</sup> Although the use of the term leukoplakia is restricted to clinical employment,<sup>1</sup> it can be applied both as a provisional and a definitive diagnosis.<sup>4</sup>

Oral leukoplakia holds a very important aspect to clinicians in that it is regarded as the most common precancerous lesion of oral mucosa.<sup>5</sup> It represented approximately 85% of oral malignancies.<sup>10</sup> Leukoplakia had a wide range of malignant transformation rates, varying from 0.13 to 18% of cases.<sup>11,12</sup> This discrepancy was largely due to the use of different definitions,

terminologies<sup>5</sup> and varying follow-up periods among studies.<sup>13</sup>

Leukoplakia can be divided roughly into two clinical types, the homogeneous and the non-homogeneous leukoplakia. Homogeneous leukoplakia is defined as a predominantly white lesion of uniform flat, thin appearance that may exhibit shallow cracks and has a smooth, wrinkled or corrugated surface with an overall consistent texture. Lesion with predominantly white or red and white that may be irregularly flat, nodular or exophytic is entitled non-homogeneous leukoplakia.<sup>4</sup> The term “nodular or speckle leukoplakia” is also used to describe non-homogeneous leukoplakia that displays eroded, erythematous, and nodular surface.<sup>1,14</sup> In addition, the lesion with papillary or wart-like surface is called “verrucous leukoplakia”.<sup>14,15</sup>

### **Proliferative verrucous leukoplakia**

Proliferative verrucous leukoplakia (PVL) is a specific form of oral leukoplakia, first described by Hansen et al<sup>7</sup> in 1985 as a disease which exhibited strong tendency to develop into carcinoma. It can present with a wide range of clinical-pathologic characteristics. The initial lesion of PVL begins as a solitary homogeneous leukoplakia, and the microscopic examination reveals only simple hyperkeratosis. However, over an extended period of time, the lesion becomes enlarged, diffuse and presents multifocally. The treatment of such lesion by surgical excision results in recurrence. Some areas later exhibit exophytic, papillary or wart-like appearance and are sometimes accompanied by erythematous component. PVL is a slow-growing, irreversible and persistent lesion. It is resistant to all kinds of conservative treatment. Recurrence of PVL can be expected with the rate of 86.7% after treatment by conventional surgery or laser surgery.<sup>16</sup> Eventually, a large number of lesions will

transform into verrucous carcinoma or squamous cell carcinoma.<sup>7,9</sup> The reported rates of malignant transformation by Hansen et al<sup>7</sup> and Silverman et al<sup>9</sup> were 86.67% and 70% of cases, respectively.

PVL represents a continuum of disease, ranging from a hyperkeratosis at one end to an invasive squamous cell carcinoma, capable of local and distant metastases, at the other.<sup>7,8</sup> Because this is the spectrum of disease expression, the definitive diagnosis of PVL at first evaluation of the clinical and histopathologic findings may not be possible.<sup>7</sup> It is usually until the clinical features of multifocal, exophytic or papillary appearance develop together with persistent and recurrent behavior that help clinicians consider the diagnosis of PVL.<sup>1</sup> In addition, the slow-growing pattern and lack of painful symptom of this lesion may mislead both patients and clinicians into something less aggressive than it actually is.<sup>7,8</sup>

The use of flow cytometry might possibly be helpful in detecting patients with early PVL, as highlighted in the study by Kahn et al.<sup>17</sup> They found the DNA aneuploid cell lines in all their patients when analyzed by this method on the paraffin-embedded specimens of PVL. The abnormal DNA index of these cell lines also remained constant throughout the monitoring period. This would subsequently enable clinicians to perform the proper treatment early in the course of this disease.

Recently, Fettig et al<sup>18</sup> reported 10 patients with features of oral leukoplakia consistent with PVL clinically and pathologically, except that these lesions presented only on tooth-bearing area. They coined the term “Proliferative verrucous leukoplakia of the gingiva (PVLG)” and regarded it as a subset of PVL. PVLG was described as a solitary or regional leukoplakia with recurrent, persistent and progressive

behavior. The lesion was confined to free or attached gingiva, particularly in the anterior region. Multiple lesions, the characteristic of typical PVL, did not develop.

In addition, an unusual case of PVL with cutaneous involvement was also reported. The lesions were clinically white plaques which extended from mandibular vestibule to lip vermillion and onto the skin of lower lip and chin.<sup>19</sup>

### Prevalence and distribution

PVL can be found in patients over a wide age range. The age of patients at first biopsy, reported in the literature, ranged from 22 to 90 years old<sup>7-9,17-25</sup> with the majority of cases being over 60 years old.<sup>7,9,16,20,25</sup> Many preceding published series of PVL reported the strong female predilection. The ratio of women to men was as high as 4 to 1.<sup>7,9,16,25</sup> This gender distribution was very different from that of typical oral leukoplakia in which women were more than 2 times outnumbered by men.<sup>4,6,13</sup>

The most common locations of PVL were buccal mucosa and gingiva.<sup>9,16,20</sup> This was consistent with the predominant intraoral sites of leukoplakia.<sup>1,26</sup> PVL occurring on the gingiva and tongue showed the greatest tendency for malignant transformation.<sup>9</sup>

### Etiology

From the epidemiologic data, natural history and clinical-pathologic variation of PVL, it seems reasonable to point out that PVL is a multifactorial disease.<sup>1,9</sup> However, several contributing factors, generally found to be associated with oral leukoplakia as well as oral squamous cell carcinoma (OSCC), could not be demonstrated in PVL.<sup>2,7-9,18,21,27</sup>

Tobacco has been accepted to be the most significant risk factor in patients with oral leukoplakia.

There was a well-known dose-response relation of oral leukoplakia and tobacco,<sup>28,29</sup> emphasizing the causative role of tobacco in the pathogenesis of oral leukoplakia. However, such a strong connection could not be established in PVL patients. The study by Silverman et al<sup>9</sup> and Bagan et al<sup>16</sup> indicated that only 31% and 21.1% of PVL patients used tobacco, respectively. Likewise, even though candidiasis was thought to be one of the etiologic factors of oral leukoplakia, there was no apparent association between PVL and the presence of candida in the biopsy specimens.<sup>9</sup>

The concept of field cancerization was applied to PVL due to the high tendency to develop multiple OSCCs in the same patients. More than 50% of the PVL cases that developed OSCC continued to develop further primary tumors in different areas of the oral cavity.<sup>21</sup> However, the carcinogenic agents, which influenced such event, still need to be determined.

Kannan et al<sup>25</sup> reported the increased transforming growth factor- $\alpha$  (TGF- $\alpha$ ) immunoreactivity in PVL, compared to the normal oral epithelium. They stated that this subcellular biological change might occur relatively early in PVL and continue through the course of disease. More studies are required to help clarify the role of this mitogen in the progress of PVL.

The association between PVL and human papillomavirus (HPV) was particularly suspected because of the papillary or verrucous clinical and histopathologic features, seen in PVL-associated lesions.<sup>27,30</sup> Several studies attempted to study the role of HPV in PVL, and the results were still diverse.<sup>27,30,31</sup> Palefsky et al<sup>27</sup> first reported the strong relationship between HPV and PVL. They found that 8 of the 9 PVL tissues were positive for HPV infection, and of these 8 positive lesions, 7 were positive to HPV type 16. They sug-

gested that HPV type 16 infection might play a role in the pathogenesis of PVL-associated oral dysplasia and possibly oral cancer. The HPV proteins, called E6 and E7, can bind and inactivate the protein products of two key tumor suppressor genes of the host cells, the p53 and the Rb protein respectively, and are thought to take part in the development of OSCC in some patients.<sup>32</sup>

However, the study of the p53 expression and HPV integration in PVL by Gopalakrishnan et al<sup>31</sup> failed to establish such association. Only 2 of the 10 PVL cases in their study were positive to HPV infection. Although there were increased p53 protein accumulations in 8 of the 10 cases, no mutation was identified. They concluded that the p53 immunohistochemistry, p53 gene mutations and human papillomavirus infection prevalence did not provide both a means to differentiate between leukoplakia and carcinoma and a predictive test for progression of leukoplakia to carcinoma. Recently, the data from Campisi et al<sup>30</sup> also found no significant difference in the risk of HPV infection between PVL and oral leukoplakia. Therefore, further studies are needed to elucidate the role, if any, of HPV and to define its actual mechanism in the pathogenesis of PVL.

## Histopathologic features

As described earlier, PVL is a disease with a continuum of clinical-pathologic expressions.<sup>1,7</sup> Hansen et al<sup>7</sup> proposed the histopathologic stages of PVL, ranging from clinical flat leukoplakia, verrucous hyperplasia, verrucous carcinoma, papillary squamous cell carcinoma and less differentiated squamous cell carcinoma. The intermediate and the combination between these stages were also included. However, Batsakis et al<sup>33</sup> argued that the papillary squamous

cell carcinoma should be excluded from the spectrum of PVL because the previous cases reported in the literature might not represent the true papillary squamous cell carcinoma, and the usual site of this disease was the oropharynx, not the oral cavity.

The initial lesion of PVL represents only simple hyperkeratosis with either absent or mild dysplasia. The lesion that exhibits severe dysplasia on first microscopic examination is not a suitable candidate for PVL.<sup>7,34</sup> Such lesion would expect be progress rapidly to squamous cell carcinoma and may or may not be papillary or verrucous in nature.<sup>7</sup>

Verrucous hyperplasia is a histologically defined lesion. Because its clinical appearance is vaguely recognized, the diagnosis of this lesion should be restricted only in the histopathologic diagnosis.<sup>7,33,35</sup> Verrucous hyperplasia was first described by Shear and Pindborg<sup>36</sup> in 1980. It is believed to be the irreversible precursor of verrucous carcinoma. The histopathologic features of both lesions are very similar and sometimes indistinguishable, especially if the biopsy specimens are inadequate.<sup>36,37</sup>

Two types of verrucous hyperplasia, the sharp and the blunt form, were described.<sup>36</sup> As their names implied, the verrucous projections in the sharp form are long, narrow and heavily keratinized, while the short, blunt and less keratinized are seen in the blunt form. The combination of both types can also be found in the same lesion. The rete ridges are often broad and blunt; however, the sharp and narrow form is also seen. The underlying connective tissue is usually infiltrated by chronic inflammatory cells.

The important feature which separates verrucous hyperplasia from verrucous carcinoma is the location of the thickened epithelium.<sup>36,37</sup> The rete ridges of

verrucous hyperplasia lie above the normal epithelium adjacent to the lesion, whereas the more downward rete ridges are anticipated in verrucous carcinoma.<sup>36</sup> Therefore, the biopsy specimen involving the normal mucosa near the margin of the lesion is crucial for the definitive diagnosis.

Verrucous carcinoma demonstrates the papillary or verruciform epithelial proliferation with characteristically broad, bulbous and pushing rete ridges, often extending deep and retracting the margin of uninvolved epithelium down into the submucosa. The parakeratin or orthokeratin pluggings are apparent between the exophytic epithelial projections. The epithelial cells are well-differentiated, showing no or only minimal dysplastic change. No actual connective tissue invasion is seen. In addition, the infiltration of chronic inflammatory cells is noticed subjacent to the epithelium.<sup>38,39</sup>

Papillary squamous cell carcinoma is the lesion found predominantly in the oropharynx, larynx and sinonasal tract. Microscopically, it represents a squamous epithelial proliferation with papillary architecture. The epithelium shows marked dysplasia, like that of carcinoma in situ and is usually non-keratinized. Some authors discarded papillary squamous cell carcinoma from the histopathologic spectrum of PVL.<sup>33</sup>

The end of the continuum of PVL is the invasive squamous cell carcinoma of variable differentiation. The distant metastasis and regional lymph node involvement were also reported.<sup>20</sup> Finally, it should be emphasized that all the lesions in each histopathologic stage of PVL are indistinguishable from non-PVL associated lesions of the same type.<sup>27</sup> Therefore, it is important to evaluate the patient's history, clinical information, together with the histopathologic findings in order to make the diagnosis of PVL.

## Treatment

Proliferative verrucous leukoplakia is extremely difficult to control.<sup>20</sup> A variety of therapeutic approaches, such as conventional surgery, laser surgery, radiation therapy and chemotherapy, have been applied to patients with PVL and ended up with disappointing outcomes.<sup>1,7-9,20,21</sup> Zakrzewska et al<sup>20</sup> reported 100% recurrence rate at the site, previously treated by surgical excision. This exceedingly high recurrence rate is believed to be the result of subcellular molecular changes in the oral epithelium that cannot be detected clinically and histopathologically in the early lesion of PVL, leading to the insufficient surgical margin.<sup>9</sup>

The laser surgery has shown several advantages over the conventional surgical approach; for instance, the rapid and precise removal of lesional tissue, easy control of bleeding, good patient acceptance, low complications and favorable healing.<sup>40</sup> However, in patients with PVL, the treatment results still remain unsatisfactory. The lesions often recur within a matter of months after treatment.<sup>1,7,9,16,20</sup>

Because PVL lesions are usually wide-spread and present on multiple areas of the oral cavity, the total surgical excision of all lesions is unlikely.<sup>1</sup> In addition, the advanced age of most patients makes the control of complications even more difficult.<sup>7</sup>

The radiation therapy and chemotherapy were failed to permanently remove the PVL. Several studies reported the limited success of both treatment modalities with frequent recurrences and development of new lesions.<sup>7,9,16,20,24</sup>

Some chemical agents, in particular vitamin A, vitamin A analogues and antioxidant nutrients (vitamin E and beta carotene), were found to be effective in reversing some oral leukoplakias;<sup>41</sup> however, they had

only temporary effects and showed very minimal, if any, benefits in PVL patients.<sup>7,9,24</sup> Similarly, Vigliante et al<sup>24</sup> reported a case with no improvement of PVL lesions after topical application of bleomycin 0.5 or 1% solution. This drug was previously shown to be useful in treating oral leukoplakias.

In patients with HPV-associated PVL, Femiano et al<sup>42</sup> reported a significant improvement of the treatment outcome by using an antiviral agent, named methisoprinol. Methisoprinol is able to inhibit viral replication as well as to promote anti-viral cell-mediated responses, and it may have some efficacy against HPV-related lesions. The follow-up period in their study was 18 months, and they found that only 16% of cases treated by combined therapy of surgery and methisoprinol recurred after treatment, compared to 72% of cases treated by surgery alone. However, more case-control studies with long term of follow up are necessary to substantially support the definite effectiveness of this drug in enhancing the treatment outcomes of patients with HPV-associated PVL.

Zakrzewska et al<sup>20</sup> reported 5 patients who underwent photodynamic therapy, and 3 had no recurrence at the site of treatment. They stated that photodynamic therapy might be a very suitable method for PVL patients, because multiple lesions could be treated simultaneously with relatively low morbidity and no residual scarring. The trial of this type of treatment yet needs to be further studied.

Several authors suggested the aggressive management of PVL as early as possible in order to completely eradicate both the diseased and undetected altered tissue.<sup>8,9,20</sup> Since the diagnoses of PVL are usually made retrospectively, the treatment results as well as the prognoses of patients are still poor, especially in late



PVL when wide-spread and multiple lesions occur.<sup>7,8</sup> Fettig et al<sup>18</sup> stated that after several recurrences by conservative scalpel or laser excision, a rather aggressive treatment such as local block resection seemed to be the only curative procedure in patients with PVLG. In addition, it is essential to closely follow up patients to investigate the recurrence of previously treated lesion, the development of new ones and the possible signs of malignant transformation.<sup>20</sup>

### Conclusion

Proliferative verrucous leukoplakia is an uncommon form of oral leukoplakia with undetermined origin. It displays the high rates of malignant transformation and mortality. In contrast to those of other forms of oral leukoplakia as well as oral squamous cell carcinoma, PVL often affects the elderly women with no history of tobacco use. The most common locations are gingiva and buccal mucosa. PVL represents a disease with a wide spectrum of clinical and histopathologic presentations, ranging from simple hyperkeratosis with or without dysplasia to verrucous or squamous cell carcinoma. Clinicians should examine their patients carefully to inspect any potential precancerous lesions, since the early diagnosis is very important to the management of patients with PVL. All available information from patient's history, clinical examination and histopathologic findings are needed, in order to make the diagnosis of PVL. Finally, the long term follow-up with regular interval is mandatory to investigate any recurrences after treatment or occurrences of new lesions.

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# โพรลิเฟอเรทีฟ เวอร์รูคัส ลิวโคเพลเคีย: บทความปริทัศน์

เอกรัฐ ภัทรธราธิป ท.บ.

ภาควิชาทันตพยาธิวิทยา คณะทันตแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

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## บทคัดย่อ

บทความนี้นำเสนอโรคโพรลิเฟอเรทีฟ เวอร์รูคัส ลิวโคเพลเคีย (พีวีแอล) ซึ่งเป็นรูปแบบหนึ่งของลิวโคเพลเคียของช่องปาก ที่แสดงพฤติกรรมก้าวร้าวเนื่องจากอัตราการกลับเป็นซ้ำและอัตราการเปลี่ยนแปลงเป็นเนื้อร้ายสูง สาเหตุของการเกิดโรคยังไม่ทราบแน่ชัด ความชุกและการกระจายของรอยโรคชนิดนี้แตกต่างจากลิวโคเพลเคียชนิดอื่น และมีลักษณะทางคลินิกที่หลากหลาย ขึ้นอยู่กับระยะการพัฒนารอยโรค พีวีแอลต้องการรักษาเกือบทุกชนิด ทำให้การควบคุมโรคทำได้ยาก โดยเฉพาะระยะท้ายๆ ซึ่งรอยโรคมักเกิดขึ้นหลายตำแหน่ง การวินิจฉัยผู้ป่วยแต่เริ่มแรกเป็นสิ่งจำเป็น ดังนั้น ทันตแพทย์จึงควรรู้จักและคุ้นเคยกับลักษณะการแสดงออกของโรคนี้

(ว ทันต จุฬาฯ 2548;28:59-68)

**คำสำคัญ:** พีวีแอล; โพรลิเฟอเรทีฟ เวอร์รูคัส ลิวโคเพลเคีย; ลิวโคเพลเคียของช่องปาก

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