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## Proliferative Verrucous Leukoplakia – diagnostic pitfalls and suggestions

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Sir,

Since its introduction in 1985 by Hansen et al (1), Proliferative verrucous leukoplakia (PVL) remains an enigmatic and difficult to define sub entity of leukoplakia. Due to poor definition of oral leukoplakia and the lack of reproducible criteria for the adjectives “proliferative” and “verrucous”, the data in the literature on oral PVL are hardly comparable. A number of the reported cases have initially presented as a solitary, otherwise inconspicuous flat homogenous leukoplakia, while others present with multiple involved sites at time of diagnosis. Whatever be the initial presentation, recurrence after treatment is the rule. Soon after first treatment the lesions appear again, not only at the previous site but also at new sites– the gingiva being most commonly affected {Silverman et al. 1997 (2), Fettig et al. 2000 (3) and Bagan et al. 2003 (4)} and hence the term PVLG was introduced. The proliferative effect of PVL was explained on basis of the high rate of field cancerization existing in PVL patients {Bagan et al. 2004 (5)}. It was noted that there is usually a time lag between the appearances of new tumors in the same patient. This suggests that PVL might have an infectious etiology- possibly a viral infection. Although several workers {(Palefsky et al. 1995 (6), Gopalakrishnan et al. 1997 (7), Eversole 2000 (8)} have suggested that HPV might have a role in

the pathogenesis of PVL, Bagan et al. in 2007(9) failed to find HPV in their group of patients and suggested that there is no association of PVL with HPV. Rather recently, in 2008 Bagan et al. (10) detected the presence of EBV in a large percent of their patient group suggesting an etiologic role in the pathogenesis and recurrence of PVL. Despite such extensive works, the etiology of PVL is still as enigmatic as the disease itself.

Although on one hand the entity of a recurrent, progressive verrucal lesion cannot be questioned, it is not correct to include several lesions as mentioned by Hansen et al in one category as PVL. While it is accepted that approximately 5% of leukoplakias will transform into cancer in an average period of 5 years, PVL has an almost 100% rate of malignant transformation over an extended follow-up period. To group two such lesions in one broad category of “Proliferative leukoplakia” is itself not justified. Moreover, the term “leukoplakia” masks the recurrent and progressive nature of the lesion and can put the clinician into false sense of comfort until there is widespread disease and advent of carcinoma.

It is also seen frequently now, that for a case of a recurrent verrucal lesion, several pathologists give the diagnosis of PVL which is wrong in the first place as it is a clinical diagnosis. The problem is further worsened by the fact that the stage of PVL is usually not mentioned

by the pathologists. PVL as described by Hansen develops through a histopathological continuum encompassing 10 stages- from hyperkeratosis to squamous cell carcinoma. Thus, in such a case, where the pathologist gives a diagnosis of PVL (without a stage) the surgeon may get a very benign impression of a serious lesion or may take a wait and watch approach for a serious lesion. Hence, if a pathologist gives a diagnosis of PVL, it is necessary that the stage of PVL must be mentioned. Later, Batsakis et al. (11) proposed only 4 stages with intermediates for development of PVL further complicating the issue of diagnosing the exact stage of the disease. Thus, it is strongly recommended that instead of merely declaring the disease as PVL, the pathologists should give a more descriptive diagnosis e.g. a verruciform lesion showing areas of dysplasia and/ or verrucouscarcinoma and/ or squamous cell carcinoma. This will present the true picture to the surgeon and adequate treatment will be rendered.

The ambiguity of PVL is further aggravated because there are no criteria that dictate how extensive the leukoplakic changes should be or how many or which oral sub sites should be involved or how many recurrences should have occurred in order to qualify for the diagnosis of PVL. This lack of exact diagnostic criteria is a prime reason due to which patients of PVL do not get correct treatment on time and even the concept of PVL as an entity has been questioned. Hence it is necessary that the concept of PVL should be modified and quantified so that a prompt and better treatment can be rendered to these patients, thus improving their prognosis. All the patients with a recurrent white lesion, however innocuous in appearance, should be suspected as PVL and should be closely followed e.g. at intervals of six months. In fact, the absence of epithelial dysplasia in initial stages of histopathologic spectrum of PVL, prevents such a white lesion from being recognized as potentially malignant and being suited for an aggressive treatment (12). Jon Sudbø et al. (13) had proposed that DNA analysis of cells of leukoplakia can be used to predict the risk of malignant transformation. Kahn et al. (14) used flow cytometric analysis (DNA aneuploidy) to successfully predict the seriousness of lesions clinically and histologically appearing innocuous. Hence, keeping in mind, the welfare of patient and importance of early diagnosis for better treatment and prognosis of PVL, we strongly recommend DNA analysis of all innocuous looking recurrent white lesions.

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. Thus Fetting et al. (3) 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.

## References

1. Hansen LS, Olson JA, Silverman S Jr. Proliferative verrucous leukoplakia. A long-term study of thirty patients. *Oral Surg Oral Med Oral Pathol.* 1985;60:285-98.
2. Silverman S Jr, Gorsky M. Proliferative verrucous leukoplakia: a follow-up study of 54 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1997;84:154-7.
3. Fetting A, Pogrel MA, Silverman S Jr, Bramanti TE, Da Costa M, Regezi JA. Proliferative verrucous leukoplakia of the gingiva. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000;90:723-30.
4. Bagan JV, Jimenez Y, Sanchis JM, Poveda R, Milian MA, Murillo J, et al. Proliferative verrucous leukoplakia: high incidence of gingival squamous cell carcinoma. *J Oral Pathol Med.* 2003;32:379-82.
5. Bagan JV, Murillo J, Poveda R, Gavalda C, Jimenez Y, Scully C. Proliferative verrucous leukoplakia: unusual locations of oral squamous cell carcinomas, and field cancerization as shown by the appearance of multiple OSCCs. *Oral Oncol.* 2004;40:440-3.
6. Palefsky JM, Silverman S Jr, Abdel-Salaam M, Daniels TE, Greenspan JS. Association between proliferative verrucous leukoplakia and infection with human papillomavirus type 16. *J Oral Pathol Med.* 1995;24:193-7.
7. Gopalakrishnan R, Weghorst CM, Lehman TA, Calvert RJ, Bijur G, Sabourin CL, et al. Mutated and wild-type p53 expression and HPV integration in proliferative verrucous leukoplakia and oral squamous cell carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1997;83:471-7.
8. Eversole LR. Papillary lesions of the oral cavity: relationship to human papillomaviruses. *J Calif Dent Assoc.* 2000;28:922-7.
9. Bagan JV, Jimenez Y, Murillo J, Gavalda C, Poveda R, Scully C, et al. Lack of association between proliferative verrucous leukoplakia and human papillomavirus infection. *J Oral Maxillofac Surg.* 2007;65:46-9.
10. Bagan JV, Jimenez Y, Murillo J, Poveda R, Diaz JM, Gavalda C, et al. Epstein-Barr virus in oral proliferative verrucous leukoplakia and squamous cell carcinoma: A preliminary study. *Med Oral Patol Oral Cir Bucal.* 2008;13:E110-3.
11. Batsakis JG, Suarez P, El-Naggar AK. Proliferative verrucous leukoplakia and its related lesions. *Oral Oncol.* 1999;35:354-9.
12. Van der Waal I, Reichart PA. Oral proliferative verrucous leukoplakia revisited. *Oral Oncol.* 2008;44:719-21.
13. Sudbø J, Kildal W, Risberg B, Koppang HS, Danielsen HE, Reith A. DNA content as a prognostic marker in patients with oral leukoplakia. *N Engl J Med.* 2001;344:1270-8.
14. Kahn MA, Dockter ME, Hermann-Pettrini JM. Proliferative verrucous leukoplakia. Four cases with flow cytometric analysis. *Oral Surg Oral Med Oral Pathol.* 1994;78:469-75.