

Proliferative Verrucous Leukoplakia

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Background

Proliferative verrucous leukoplakia (PVL) is an uncommon form of progressive multifocal leukoplakia with a high rate of malignant transformation to either squamous cell cancer or verrucous carcinoma and a high probability of recurrence.

Pathophysiology

The etiology of proliferative verrucous leukoplakia is unknown. An association with human papillomavirus (HPV) infection, particularly strains 16 and 18, has been implicated in some cases.^[1] Furthermore, because multiple cancers occur in proliferative verrucous leukoplakia-afflicted patients (ie, field-cancerization phenomenon), this suggests an infectious agent is responsible for the tumors. However, this link is inconsistently present in investigated cases.^[2, 3, 4, 5]

Furthermore, the cell cycle regulatory genes *p16^{INK4a}* and *p14^{ARF}* are noted to be altered in lesions of proliferative verrucous leukoplakia.^[6] However, a role for the *TP53* gene mutation or inactivation has not been found in the pathogenesis of proliferative verrucous leukoplakia.^[7]

Increased expression of immunoreactive tumor growth factor-alpha has been noted in lesions of both proliferative verrucous leukoplakia and oral squamous cell cancer, but not in healthy oral mucosa.^[8] Tumor growth factor-alpha is a potent mitogenic polypeptide expressed by epithelial cells under physiologic conditions and by activated macrophages and eosinophils in certain pathologic conditions.

Flow cytometric analysis of archived lesions of proliferative verrucous leukoplakia has shown evidence of aneuploid cell lines, with DNA indexes remaining constant throughout the course of disease in most cases. Thus, flow cytometry has been proposed as a tool to help identify lesions of proliferative verrucous leukoplakia early in the course of the disease.^[9] More recently, it has been suggested that a combination of image-based DNA ploidy analysis and evidence of dysplasia on histology may be useful in predicting which lesions are likely to undergo malignant transformation.^[10]

Furthermore, unlike other forms of oral leukoplakia and oral squamous cell cancer, proliferative verrucous leukoplakia lesions are not strongly associated with a history of alcohol or tobacco use or the presence of candidiasis, nor has evidence of immunodeficiency or vitamin deficiency been linked.^[11, 12, 13, 14, 15]

Epidemiology

Frequency

United States

Proliferative verrucous leukoplakia is an uncommon variant of oral leukoplakia, occurring in less than 1% of adults.

International

No data on the worldwide incidence of proliferative verrucous leukoplakia are reported.

Race

Although most studies of proliferative verrucous leukoplakia have been reported from western populations in the United States, Great Britain, Spain, and Italy, cases of possible proliferative verrucous leukoplakia have been reported in people of Indian and Chinese origin living in Malaysia.^[16]

Sex

Most cases occur in females, with a female-to-male incidence ratio of approximately 4:1.

Age

Proliferative verrucous leukoplakia is usually seen in adults older than 40 years. The peak incidence occurs in women aged 60-70 years.

Prognosis

Nearly all cases of proliferative verrucous leukoplakia develop into malignancy. Proliferative verrucous leukoplakia-associated cancer mortality rates reportedly are 39-43%.

Patient Education

Patients with proliferative verrucous leukoplakia should avoid other known factors associated with development of oral squamous cell carcinoma, such as tobacco, alcohol, and betel.

Clinical Presentation

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