mini-review

Current Evidence in Diagnosis and Treatment of Proliferative Verrucous Leukoplakia

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Ann Saudi Med 2012; 32(4): 412-414

DOI: 10.5144/0256-4947.2012.412

Proliferative verrucous leukoplakia is multifocal and progressive lesion with a high rate of malignant transformation. This short review highlights the diagnosis, traditional treatment and the current management of the disease. A MEDLINE search for the specific English word including proliferative verrucous leukoplakia in the last two years (2009-2010). This study indicates the current evidence for the diagnosis and the management of proliferative verrucous leukoplakia to help the specialist in this domain for early diagnosis of proliferative verrucous leukoplakia according to the new criteria of diagnosis to prevent the recurrence and any malignant transformation.

White lesions are relatively frequent in the oral cavity with a prevalence of approximately 24.8% according to Axéll.[1] Among them is oral leukoplakia with a prevalence 0.2 to 3.6%.[1-5] Leukoplakia was described by the WHO as a "precancerous lesion"[6] and recently this terms was substituted by the terms "Potentially malignant disorders".[7] Its malignant transformation rate varies from 0.1% to 17.5%.[8-10] Proliferative verrucous leukoplakia (PVL) is a distinct clinical form of oral leukoplakia first described in 1985 by Hansen et al.[11] The WHO also described PVL with a high rate of malignant transformation.[12] PVL is multifocal and progressive lesions are seen frequently in women characterized by a recurrence and a high rate of transformation into oral cancer resistant to all forms of treatment.[13]

Proliferative verrucous leukoplakia is more common in elderly women who have had lesions of leukoplakia for many years.[11] Frequently in women and elderly patients over 60 years with a ratio of women/men of 4/1. Smoking and drinking have not been directly associated with PVL.[14]

Clinical characteristics

PVL may appear on any soft tissue of the oral cavity and may be present as single or multifocal growths involving several oral sites. Some have found that the buccal mucosa is the most frequent location in women and the tongue in the men.[15] The area most frequently affected with PVL were the lower gingival, tongue, buccal mucosa, alveolar ridge.[16] Although some research has proposed four stages of development to PVL, which starts as a simple hyperkeratosis without epithelial dysplasia, verrucous hyperplasia, verrucous carcinoma, and conventional carcinoma.[17,18]

Etiopathogenesis and Diagnosis

PVL is of uncertain etiology but may be associated with human papillomavirus (HPV) infection. They suggest that HPV-16 infection may play an important role in theses lesions,[19,20] although some have failed in patients with PVLG to detect HPV-DNA by PCR.[21] It appears that any association between PVL and HPV may be present in some but not all lesions of PVL.[22] The diagnosis of PVL is based on clinical data as a progressive evolution of homogeneous leukoplakia that spreads to different locations with changes in appearance. Histopathology may help to distinct the stage of the disease as described before.

Management

Because of the relentless growth pattern associated with

PVL and its propensity to develop into carcinoma[11,16] early and aggressive treatment of such a lesion is recommended.[15,21] There is no effective management reported. Schoelch et al reported laser treatment using CO_2 and Nd:YAG (neodymium-doped yttrium aluminum garnet), but found a high rate of recurrences of 83%.[23] Bagan et al found a recurrence rate of 86.7% after treatment with CO^2 laser and or/scalpel surgery.[14]

Nonsurgical therapeutic approaches for PVL have been considered such as external beam radiation therapy, cryotherapy, and topical vitamin therapy, but none has proven to be beneficial.[15,18] Early trials of topical chemotherapy with bleomycin have been assessed.[24,25] Surgical shave followed by cryosurgery and photodynamic therapy have also been suggested.[26,27] Antiviral methisoprinol appeared to offer a significant benefit.[28] In the future, anti-HPV, anti-TGF, and pro-apoptotic management strategies may be considered.[29]

Evolution

PVL is an unknown disease in which no etiological factors have been found. The diagnostic criteria are not well established. It is characterized by a high rate of recurrence after treatment and also by malignant transformation in nearly 74% of cases with a tendency for several oral cancer to appear.[30] Bagan et al found recurrences after treatment 86.7% of cases, new lesions during follow up in 83.3%, and oral cancer eventually in 63.3% with a high incidence of the gingival type, which emphasizes the importance of PVL awareness for periodontists.[14]

Saito et al 1999 found that the widespread multiples oral leukoplakias have a higher potential for the development of cancer and probably most of multiple oral leukoplakia develop to PVL.[31]

Ghazali et al[32] establish the following criteria for the diagnostic of PVL:

1) Lesion starts as homogeneous leukoplakia with evidence of dysplasia.
2) With time some areas of the leukoplakia becomes verrucous.
3) Disease progresses to multiple lesions at the same or different site.
4) With time disease progresses into different histological stages.
5) Appearance of new lesion after treatment.
6) Clearly histologically PVL after follow up periods of no less than one year.

On other hand Gandolfo S et al[33] established the following criteria:

1) Homogenous plaque that progresses over time to exophytic, diffuse, multifocal lesions with the verrucous epithelial growth pattern.
2) Histopathologically changes from a simple hyperkeratisis without dysplasia to verrucous hyperplasia, verrucous carcinoma or oral squamous cell carcinoma.

Recently Bagan et al 2010[34] also proposed a set of diagnostic criteria to allow for the early identification of PVL cases. The proposal includes five major criteria and four minor criteria as the following:

Major criteria (MC):

1) A leukoplakia lesion with more than two different oral sites, which is more frequently found in the gingival and alveolar processes and palate.
2) The existence of a verrucous area
3) The lesions spread or become engrossed during development of the disease.
4) Recurrence in a previously treated area.
5) Histopathologically, there can be simple epithelial hyperkeratosis to verrucous hyperplasia, verrucous carcinoma or oral squamous cell carcinoma.

Minor criteria (mc):

1) An oral leukoplakia lesion that occupies at least 3 cm when adding all the affected areas.
2) The patient is female
3) The patient (male or female) is a nonsmoker
4) A disease evolution more than 5 years.

In order to make the diagnosis of PVL, it was suggested that one of the two following combinations of the criteria mentioned before were met: three major criteria (being E among them) or two major criteria (being E among them) + two minor criteria.

Conclusion

PVL is a persistent and progressive oral lesion that require early and aggressive treatment to increase the chances of favorable outcome. Therefore, early diagnosis is recommended as well as consensus on diagnostic criteria, which improves therapeutic approaches.

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