Oral Proliferative Verrucous Leukoplakia

Subjects: Oncology
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Proliferative verrucous leukoplakia (PVL) was recognized in 2005 by the World Health Organization as a rare subtype of true oral leukoplakia, with unknown etiology. Since its first description in 1985, several diagnostic criteria have been proposed over the years.

Keywords: Oral Proliferative Verrucous Leukoplakia ; oral cancer ; biopsy

1. Introduction

Proliferative verrucous leukoplakia (PVL) was recognized in 2005 by the World Health Organization (WHO) as a rare subtype of true oral leukoplakia, with unknown etiology, which mainly affects women in old age, often with a clinical history that does not include tobacco or alcohol consumption, with high risk of malignant transformation and diagnosis, usually retrospective, based on the association of clinical and histopathological aspects [1].

The expression “proliferative verrucous leukoplakia” was firstly introduced in literature in 1985 by Hansen et al. to define a lesion characterized mainly by multifocal presentation, exophytic and verruciform appearance, resistance to all therapeutic approaches, both surgical and non-surgical, high tendency to malignant transformation and progressive histological changes, evidenced in sequential biopsies, with evolution from simple hyperkeratosis, to lesions with increasing degrees of dysplasia, oral verrucous carcinoma (OVC), and conventional oral squamous cell carcinoma (OSCC) [2].

Several diagnostic criteria for PVL have been proposed over the years to help clinicians in diagnosis. In 2010, Cerero-Lapiedra et al. identified some major and minor criteria [3], which were then eliminated in 2013 by Carrard et al. [4].

Finally, in 2018, Villa et al. suggested that all the following criteria must be satisfied for a lesion to be classified as a PVL [5]:

(1) White/keratotic lesions that can be smooth, fissured, verrucous, or erythematous, with or without the presence of ulcerated areas.
(2) Non-contiguous multifocal lesions or single lesions larger than 4 cm in a single site or single lesions larger than 3 cm with the involvement of contiguous sites.
(3) Lesions that progress/expand and/or develop multifocality over time.
(4) Histopathology, which, in absence of dysplasia or carcinoma, still shows hyperkeratosis, parakeratosis, atrophy, or acanthosis with minimal or absent cytological atypia, with or without the presence of a lymphocytic band, or verrucous hyperplasia.

The most recent guidelines about the management of the proliferative verrucous leukoplakia include constant follow-up, every 3–6 months, with biopsies involving new onset red, or nodular areas, and areas of increased consistency [5].

2. Oral Proliferative Verrucous Leukoplakia

In regard to sex distribution of PVL, according to the literature [6][7][8], women were involved by PVL more (416 = 66.7%) than men, especially in old age (mean age: 70.2 years). The gingiva/alveolar ridge mucosa was found to be the most involved intraoral site by both PVL and its malignant transformation. Usually, the lesion first involves the gingiva of a single tooth, often buccally, and then extends, over time, to that of the adjacent teeth, also on the lingual and palatal sides, likely involving the interdental periodontal tissues [5]. Therefore, any gingival leukoplakia, which progressively involves other anatomical sites over the years, must be viewed with suspicion. McParland and Warnakulasuriya in 2020 reported that 19 of the 51 patients with PVL had gingival lesions at the time of the disease onset (37.2%), while, at the last follow-up, gingival involvement was found in 33 out of the 51 patients (64.7%). Similarly, among patients who underwent neoplastic evolution of PVL, most cancers arose at the gingival level [9]. Bagan et al. in 2011, in a retrospective study on 55 subjects

with PVL, found that the gingiva was the most frequently involved site by PVL (89.1% of cases), and that more than 50% of the OSCCs developed from gingival lesions [10]. Silverman and Gorsky also reported that PVLs of the gingiva, as well as those of the tongue, had a higher tendency to malignant transformation (p = 0.13), compared to those of all other oral sites [11].

Regarding the recurrence of gingival PVL, Villa et al. [5] hypothesized that it was correlated not only to clinical features, but also to a possible incomplete excision of pathological tissue, at the level of crevicular epithelium, which therefore was able to repopulate the biopsied area, leading to the progression of residual pathological cells, rather than to a real recurrence. There are only two studies describing the tongue as the most affected site of PVL malignant transformation [12][13].

The percentage of patients with malignant transformation of PVL, in the selected studies, varied from 2.5% to 100%, with a mean value of 45.8% (320 out of 699 subjects), and a mean follow-up of 7.2 years.

Women have a significantly higher risk of developing cancer from a previous PVL than men (OR 0.57, 95% CI 0.35–0.93), even considering the higher incidence of PVL in females. Only Borgna et al. [14] found a slight opposite prevalence between men and women (12:11) among PVL-related cancer patients.

A statistically higher risk of PVL transformation to OSCC rather than OVC was found, with articles by Favia et al. [15] and Upadhyaya et al. [16] being the only exceptions.

It was also found that females not only have a higher incidence of PVL with an increased risk of its malignant transformation, but they also have a statistically higher risk of PVL progression to OSCC than males.

On the other hand, the occurrence of a verrucous carcinoma seems to be more likely in men, although with no statistical significance; thus, males, in addition to being less affected by both PVL and its malignant transformation, seem to be more frequently involved by OVC rather than OSCC, which has a much lower aggressiveness than OSCC [17], although further investigation is needed to verify this datum.

It is worthy of note that patients with PVL who develop an oral cancer, in 46.5% of cases develop at least one second tumor in a different intraoral site. In this regard, Bagan et al. [18] published a retrospective comparative study between a group of 33 patients with two or more PVL-related OSCC and a group with 48 no-cancer PVL patients, and found that clinical factors associated with the possibility of belonging to group 1 were a longer follow-up and a greater number of PVL-affected oral sites. Furthermore, the time interval between the diagnosis of each carcinoma and the next was, each time, shorter, and the most involved anatomical site by the first four carcinomas was gingiva, while buccal mucosa or the tongue were more frequently involved by the fifth new carcinoma [18].

The multifocal presentation typical of PVL and the high risk of developing multiple primary oral carcinomas have been associated with the concept of field cancerization, proposed in 1953 by Slaughter et al. [19], and subsequently suggested by others [20][21], to explain the occurrence of more than one carcinoma in the same district. This theory argues that there is the presence of genetically mutated cells even beyond the area with alterations evident on clinical or histopathological examination and the main molecular alterations would involve mutations in oncogenes or tumor suppressor genes, genomic instability and loss of heterozygosity. In the case of the upper aero digestive tract, these alterations have usually been correlated with prolonged exposure to carcinogens, such as tobacco; however, since most patients with PVL are not tobacco users [2][11], probably further, but yet unidentified, mechanisms may be involved. In this regard HPV infection has also been suggested having a role both in PVL etiopathogenesis and in its malignant transformation [22][23]. Moreover, PVL has different demographic aspects than those of conventional true oral leukoplakia [6] and, frequently, a verrucous appearance, which is typical of HPV-related lesions. However, other authors did not find any statistical correlation between HPV infection and both PVL [24][25] and its progression to malignancies [16]; therefore, it is not possible to exclude or confirm a possible etiopathogenetic role of HPV.

The consumption of tobacco (smoked or chewed) and alcohol does not seem to play an important role in the onset of this lesion, differently from the true leukoplakia, for which tobacco is recognized as the only risk factor [26]. Collecting data from the individual studies analyzed, a current or previous tobacco consumption was found in 218 out of 544 patients with PVL (40%), and alcohol use in 65 out of 248 subjects (26.2%). In five studies, the number of tobacco users exceeded half of the analyzed subjects [2][27][14][16][28]. Moreover a significant number of patients with PVL malignant transformation were not smokers; Bagan et al. in 2003 reported the presence of 4 tobacco users among 19 with PVL and progression to OSCC (21.1%) and 78 among 110 patients with OSCC not preceded by PVL lesions (70.9%) [29]. Favia et al., described the presence of 11 smoking patients among 48 with PVL who developed at least one carcinoma (22.9%) [15]. Borgna et

al., in 2016, found no significant differences regarding tobacco and alcohol use between the 23 patients with PVL and malignant transformation and the 25 individuals with PVL without malignant transformation [14].

As for the etiopathogenesis of PVL-related carcinomas—in 2015, Akrish et al. hypothesized [30] that PVL-related OSCC represented a distinct entity with respect to PVL-unrelated OSCC since many features differed in the two conditions. They found PVL-related OSCC being more frequently featured by the following features: early stage of development, small tumor size, no lymph node metastases, gingiva and buccal location, local relapses or second primary tumor, and a good 4-year survival rate (100%). On the contrary, PVL-unrelated OSCC were featured by the following features: more advanced stage of development with wider tumor size, high frequency of lymph node metastases (36.7%), lingual margin and mouth floor mucosa as prevalent locations, less frequent relapses or second tumors (12.2%). This hypothesis, obviously, may have practical implications in choosing both treatment strategies and follow-up timing for OSSCs occurring in the two different conditions, although further comparative studies with wider sample sizes are needed to corroborate such a suggested point of view.

3. Conclusions

It can be stated that PVL is an aggressive lesion, which, in almost 50% of cases, undergoes malignant transformation, mainly toward OSCC. Women are more involved than men, especially in older age and with a negative history of alcohol and tobacco consumption.

Early diagnosis and constant surveillance with periodic biopsies are of paramount importance in management of PVL patients, especially when an oral carcinoma has already developed.

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