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CASE REPORT :

Proliferative verrucous leukoplakia: diagnosis and treatment update

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Abstract:

Proliferative verrucous leukoplakia (PVL) is a rare form of oral leukoplakia, characterized by an aggressive biological behavior due to the high probability of recurrence and malignant transformation. Oral mucosa and tongue are the sites most often involved. Ethiopathogenisis remains unclear and several treatment approaches have been proposed.

The aim of our work is to present a clinical case of PVL with malignant transformation, detail the diagnostic approach based on its clinical and histological features and to discuss the treatment options through a literature review.

Keywords: leukoplakia, diagnosis, oral surgery procedures, laser

Manuscript:

Introduction:

Proliferative verrucous leukoplakia (PVL) is a keratotic white lesion of the oral mucosa. It was first introduced as Florid Oral Papillomatosis by Hansen in 1985 to describe a

progressive lesion developing over time from a keratotic whitish plaque that can eventually become multi-focal, warty and confluent [1]. This special entity is characterized by:

Prevalence among women

Non association with tobacco and alcohol

The evolving concept over time

An elevated risk of malignant transformation up to 100%

High recurrence after treatment

Several treatments have been proposed trying to minimize as long as possible the high recurrence rate and to prevent malignant transformation.

Observation:

Mrs. "M.M", aged 47, followed in the dermatology department for vitiligo was referred to our oral medicine and surgery unit for “chronic lingual keratosis pathology “.

Investigation revealed no history of smoking or chewing

tobacco, no associated systemic pathology and absence of any clinical symptoms after years of progress.

Lingual lesions appeared twenty years ago and were marked by the onset of asymptomatic white patches in different places of the tongue.

Oral examination showed (Fig.1) an atrophic appearance with presence of multiple confluent hyper keratosis of the dorsum of the tongue, not removable by scraping with irregular outline and accentuated in the anterior third of the tongue. We also noticed the presence of a 1-cm

exophytic nodule, flexible on palpation at the tip of the tongue looking like a cauliflower. Erythematous areas around white lesions were also present.

Fig.1: Aspect of the dorsal side of the tongue showing cauliflower-like nodule and hyperkeratosis

Examination of the ventral surface of the tongue showed the presence at the right and left lateral edges homogeneous keratotic plaques (Figure2), whereas examination of the internal surfaces of the cheeks, gingivae, palate and lingual floor did not show any particular lesions.

Fig .2: hyperkeratotic plaques in lateral edges of the tongue

Following this clinical examination, several diagnoses were raised:

- Inhomogeneous leukoplakia associated with human papilloma virus (HPV).
- Squamous cell carcinoma
- Proliferative verrucous leukoplakia (PVL)

To confirm our diagnostic hypotheses, two biopsies were performed:

A biopsy straddling the median whitish plaque in the dorsal lingual side

An excisional biopsy with healthy tissue margins of the nodule at the tip of the tongue.

Amoxicillin 2g / day, paracetamol and an anti-septic mouthwash (0.12% chlorhexidine) were prescribed.

histological examination:

The first biopsy at the level of the plaque showed a squamous coating characterized by hyper granulosis.

and a moderate ortho keratosis with an inflammatory chorion without any cell atypia or signs of dysplasia. The diagnosis retained was that of leukoplakia.(Fig.3)

The second biopsy concerned an epithelial carcinomatous proliferation characterized by significant acanthosis with enlarged ridges pushing back the inflammatory-looking chorion without signs

of infiltration. The limits of excision were verified on several sections confirming the absence of connective tissue invasion and thereby ruling out the diagnosis of squamous or hybrid carcinoma. (Fig.3)

The diagnosis of verrucous carcinoma was retained.

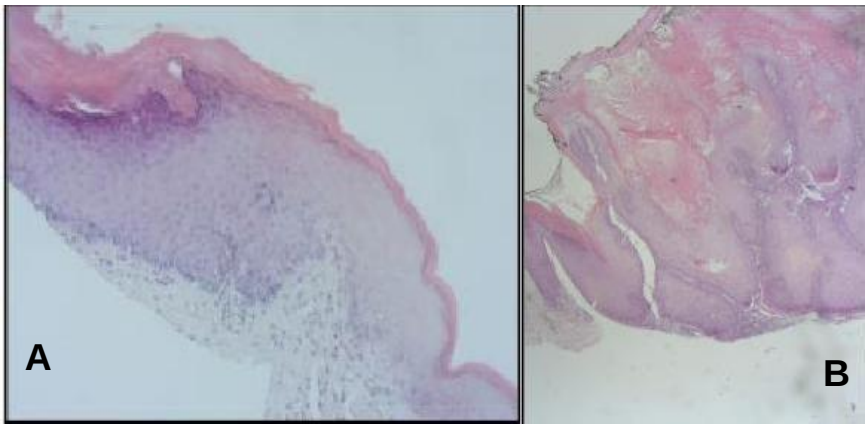

Fig.3: 3A: Histological section: HE*50 leukoplakia showing hypergranulosis and ortho keratosis, 3B: Histological section: HE*50 squamous cell carcinomatous proliferation repressing the dermis and inflammatory stroma. HE :coloration with hematoxylin eosin

Based on Carrad's classification; It was a leukoplakia showing the presence of verrucous areas involving two locations (dorsum and edges of the tongue) with an added surface area of the lesion exceeding 3 cm as well as a development period of twenty years.

By comparing clinical and histological data, the diagnosis of PVL was established.

Given the recurrent nature of the lesion, regular monitoring sessions were established; our treatment was essentially surgical based on different excisional techniques depending on the white lesions size:

Removal of keratotic plaque in the anterior third of the dorsal surface of the tongue using the CO2 laser on continuous mode 2 Watts under local anesthesia;

level II analgesic (Klipal®) was prescribed as well as a healing gel based on hyaluronic acid (KINcare®). (Fig.4)

Fig.4: plaques removal using CO2 laser and the electrical scalpel with satisfying post-operative healing

After 10 days, good healing was noted with disappearance of the plaque.

A second plaque located in the center of the tongue was removed by the electric scalpel.

Good healing was also noted, with less marked postoperative discomfort compared to the previous technique.

Given the posterior location of the third lesion associated with a gag reflex, the excision was performed under general anesthesia using an electric scalpel as well. This also was applied for leukoplakia at the lateral edges of the tongue.

15 days later, clinical examination showed a marked improvement. However unpainted areas and atrophic appearance on the dorsum of the tongue persisted. (Fig.4)

Adjunct medical treatment by application of local retinoids (Locacid®) has been considered.

The patient is regularly checked-up.

After 2 years of follow up, a relapse of a 4mm-whitish homogenous hyper keratotic plaque was noticed on the ventral surface of the tongue (Fig.5) with no malignant transformation.

Fig.5: 2 years follow up operative aspect

Discussion:

Proliferative verrucous leukoplakia(PVL) is a multifocal white lesion that may progress into verrucous and squamous cell carcinoma in most cases. At an early stage it can be confused with idiopathic leukoplakia or even hyperkeratotic lichen planus taking an homogeneous greyish-white non-verrucous appearance.

Diagnosis:

The histological variety of the lesions makes diagnosis difficult and require clinical data confrontation.

Diagnostic criteria have been first proposed by Cerero [2] classified into major and minor criteria

Carrard. criticized this classification for its lack of specificity [3] and proposed a simplified system, with the removal of major and minor criteria.

Multifocal localization presents essential diagnostic criteria. The gingival localization is

the most frequent especially at the mandible (86.7%), then comes the oral mucosa. [4]

Paradoxally in our case, only the tongue was involved with malignant transformation at the dorsum side.

Histological features:

There is not a characteristic histological definition of PVL. The diagnosis is often retrospective, made over time and requires several biopsies to show the histopathological progression of the lesion and dysplasia screening. It usually follows the onset of verrucous hyperplasia , turning into verrucous or squamous cell carcinoma.

Etiopathogenesis:

Many potential etiologies have been hypothesized, but the origin of this disease process is still unclear.

It seems that tobacco is not involved in the onset of PVL, nor in its evolution towards malignancy, unlike the majority of oral cancers [3]. Smoking patients only represent 34.3% of patients with PVL.

However, an association has been reported between PVL and high grade papilloma viruses (HPV16 and HPV 18). The qRT PCR E6 / E7 mRNA is considered the gold standard test in the detection of HPV at the sample level. [5]

Genetic studies showed aberrations in the cell cycle regulatory genes p16INK4a and p14ARF, with loss of heterozygosity. It appears to be frequent findings in 45 % PVL cases. [6]. In addition to that multiple studies showed P53 high expression in PVL samples

DNA ploidy detection has been suggested as useful in predicting the site of malignant transformation in PVL allowing early management. [7]

However, none of these studies have produced a clear insight in the etiopathogenesis of PVL.

Treatment:

PVL management differs from each patient, taking into account clinical and histological variability.

Regular clinical follow-up looking for any changes in color, surface finish, and thickness is

essential. The patient undergoes a multitude of treatments along his illness:

Areas with hyperkeratosis or verrucous hyperplasia without dysplasia or with mild dysplasia

are checked by regular biopsies or by excisional biopsy.

Areas with moderate or severe dysplasia require total resection using a scalpel, laser, photodynamic therapy, or electrosurgical unit. By far, the most widely used treatment is

surgical excision. It always allows the pathological examination of the operative part. In our case both excisional techniques (CO2 laser and electric scalpel) showed satisfying results with the same healing period except more postoperative pain and discomfort for the CO2 laser technique.

Areas with verrucous or epidermoid carcinoma require oncological resection with

healthy margins.

Many other therapeutic approaches have been proposed in the literature, including: local retinoid, beta carotene, and chemotherapy without giving any definitive cure.

As HPV seems to be implicated in the malignant transformation process, treatment with Methisoprinol which is a synthetic anti viral has been proposed. This agent, capable of

inhibiting the synthesis of viral ribonucleic acid, has shown some clinical efficacy [7]

However, to this date, there is no consensus regarding the management of PVL.

A recently conducted meta-analysis concluded there is not enough scientific evidence that any treatment strategy is able to reduce the recurrence in PVL. [8]

In our case the patient responded well to the treatment without any malignant transformation.

Prognosis and recurrence

PVL is characterized by a high rate of recurrence after treatment (87 to 100%): appearance of new lesions is often noted. Silverman and Gorsky observed an 85% recurrence rate over a follow-up period of 11.6 years in 54 patients treated with surgery alone or in combination with radiotherapy [9].

Thereby, in our case we noticed a recurrence of an hyper keratotic leukoplakia in the ventral surface of the tongue after a two-year follow up with no malignant transformation.

Conclusion:

Proliferative verrucous leukoplakia is a white lesion of the oral cavity at high risk of malignant transformation. The etiopathogenesis has been discussed, generally linked to various genetic mutations. The papilloma virus appears to be implicated.

The positive diagnosis takes into account the evolutionary character over time and it is essentially based on clinical and histological confrontation. Several treatments have been proposed in the literature, however recurrence is still observed, which implies regular clinical monitoring. Evidence-based information regarding PVL treatment is lacking, due to the paucity of data.

A better understanding of the genetic and biological factors of the pathology may provide earlier diagnosis and better management in the future.

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