Abstract

Leukoplakia is the most frequent oral potentially malignant disorder. Its diagnosis is established on clinical and histological basis. The main aim of oral leukoplakia management is to avoid malignant transformation. In order to achieve this aim there are several treatment options. These vary from total surgical removal of the lesion to “a wait and see attitude”. There is no consensus of which is the best. The decision is up to the specialist and it is adapted to every patient according to the clinical appearance and histological features.

Keywords: leukoplakia, dysplasia, treatment

Introduction

Oral leukoplakia is defined as a white patch of more than 5 mm² which doesn’t rub off and has an unknown etiology or is tobacco induced. The WHO Collaborating Centre for Oral Precancerous Lesions in 1978 defined oral leukoplakia as white patches which carry a risk of malignant transformation [1]. Later on in 2007, an Oral Medicine Working Group designed to reflect the advances in understanding of the biology of oral precancer, leukoplakia was defined as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any physical or chemical causative agent except use of tobacco [2]. Leukoplakia is a clinical term and has no specific histology. Pathological examination of leukoplakia can show hyperkeratosis, atrophy, acanthosis and different degrees of epithelial dysplasia. In evolution leukoplakia demonstrates no pattern but it has a tendency to malignant transformation. It is important that the epithelial dysplasia has no specific clinical appearance; it can be present in any apparently benign clinical white lesion. There are two major clinical forms of leukoplakia: homogenous and non-homogeneous. The homogenous type has a flat, thin and smooth surface (Figure 1).

The non-homogenous form can be speckled (white and red areas but predominantly white), verrucous (elevated, creased surface) (Figure 2) or nodular (small white nodules on the surface).

Oral leukoplakia can be a single lesion or it affects many locations thus being multifocal (Figure 3) - which is not considered a good sign.

Proliferative verrucous leukoplakia is a long term progressive form which initially is homogenous, then slowly grows and spread [3]. Lately it involves multiple mucosal areas with confluent, exophytic and proliferative features. This kind of leukoplakia is reluctant to any treatment, it has a high recurrence rate and occasionally
progress to verrucous carcinoma or squamous cell carcinoma in the range 40-100% [4].

Usually leukoplakia is used as a provisional diagnosis when at the clinical examination a white lesion cannot be certainly diagnosed as any other disease or disorder of the oral mucosa. A biopsy is necessary to establish the diagnosis. A definitive diagnosis of leukoplakia is further established when any etiological cause (other than tobacco use) has been eliminated and the histopathological examination was not specific for other disease [2].

Epithelial dysplasia is considered the most important indicator for malignant transformation. Dysplastic oral leukoplakia has a 5 times higher risk of malignancy than non-dysplastic [5]. The patients with histologically confirmed leukoplakia are reported to have no malignant transformation in 86.6% after 3 years of follow-up and 82.0% after 5 years [2]. For a period of 5 years follow-up dysplastic lesions had an incidence of malignant transformation of 41% and non-dysplastic lesions 9.5% [2].

Regardless of the advances in molecular biology, nowadays there are no reliable markers to predict the malignant transformation of oral leukoplakia [6]. The markers Ki-67 (Mib-1) and p53, are considered to be predictors for malignant transformation, but they are not generally adopted in clinical practice [6]. The treatment options for oral leukoplakia are surgical and non-surgical but there is no consensus of which is the best. The decision is adapted to every patient according to the clinical appearance (size, location) and histological features.

**Surgical treatment**

A consensus considered that surgery is the first choice in the management of oral leukoplakia [7], but it has not been demonstrated that totally removing the lesion will exclude the malignant transformation. A randomized control study which evaluated surgical treatment of leukoplakia does not show the efficiency of the surgical treatment to assess the incidence of malignisation [8]. This does not mean that surgical removal should be abandoned, mainly for histologic diagnosis [7]. The surgical treatment is a diagnostic tool which is used also in the evolution of oral leukoplakia as part of its surveillance.

There are different surgical techniques: laser, scalpel, electrocauterisation and cryosurgery.

The laser surgery has been reported as most appreciated in the last 30 years [7]. There are two main benefits of the laser: the haemostatic effect and the limited scars post treatment. This can be performed for extensive lesions. It also has reduced post operative discomfort but the main disadvantage is that the histological diagnosis of the excised area will be missing. Furthermore comparing different laser techniques, CO2 laser, neodymium: yttrium aluminum garnet (NdYAG) laser, and potassium-titanyl-phosphate (KTP) there are differences in recurrence rates (34.2%, 28.9%, and 17 %) [7,9].

Conventional surgery refers to scalpel excision of the lesion. This is followed by secondary healing in case of reduced mucosal defects or with a transposition of local mucosal flaps or even skin graft in case of large defects.
**Electrocoagulation** can be used alone or as an adjuvant to scalpel surgery. It induces thermal damage in the surrounding tissues thus causing postoperative pain and edema and tissue scarring.

**Cryotherapy** is a method which permits the destruction of lesion tissue by freezing in situ. It is carried out by either an “open” or a “closed” system [10]. The open-system cryotherapy is the direct application of cryogen on the lesion using a cotton swab [11] or by an open spray [10]. The closed-system cryotherapy brings a greater degree of control with more complex and delicate apparatus [10,11]. The main advantages of cryotherapy are the bloodless intervention, a reduced risk of post-operative infection, and a lack of scarring [12]. Some studies have shown cryotherapy as an alternative to treat oral leukoplakia [12]. During cryotherapy the ice crystals are formed in both extracellular and intracellular fluid leading to the cellular dehydration, toxic intracellular electrolyte concentration, inhibition of enzymes, protein damage. These mechanisms associated with the thermal shock induce the vacuolization of cells, their expansion and finally their rupture [12,13]. Also the vascular changes are followed by ischemic necrosis of the treated tissue and immunological responses which will produce the damage of tissue by cytotoxic immune mechanism [13].

**Medical treatment**

**Carotenoids**

Betacarotene is a vitamin A precursor. Carotenodermy (a state in which the skin becomes strongly yellowish) is the effect of excessive beta-carotene intake disappears in a few weeks after the reduction of consumption [14]. Betacarotene function is accomplished by ligation to oxygen, creating thus an unstable reactive molecule, which will reduce the damaging effects of free radicals [15]. Some studies report that clinical resolution of oral leukoplakia ranges from 4% to 54%, with dosages regimes from 20 to 90mg/day of beta-carotene in time periods from 3 to 12 months[14,16].

**Lycopene**

Lycopene is a carotenoid without provitamin A action [14]. It is a fat-soluble red pigment found in some fruit and vegetables. There is a positive relationship between lycopene consumption and a reduction in the risk of the development of degenerative diseases caused by free radicals, such as cancer and cardiovascular diseases [17]. Lycopene does bound to chemical species that react to oxygen, thus being the most efficient biological antioxidizing agent [14]. A study [18] evaluated lycopene in oral leukoplakia for a three months period, with dosages regimes from 4mg/day and 8mg/day and patients had clinical resolution 25 and 55%, respectively [14].

**Retinoic acid (Vitamin A)**

Retinoic acid includes all the natural and synthetic compounds with an activity similar to that of Vitamin A [14]. This possibility of treatment is not widely accepted due to its side effects-hypervitaminosis, toxicity, teratogenic effects, and alterations in various organic systems [14].

The topical use of 13-cis retinoic acid has been shown to be effective in resolving oral leukoplakia [15,19]. But they are limited because recurrences appear after short periods of cessation of the treatment [14,15].

In the systemic use with dosage of 300,000 IU of retinoic acid , a clinical resolution of the 50% has been demonstrated [14].

In a recent study the results obtained on using topical retinoid for the treatment of proliferative verrucous leukoplakia, involving variable concentration of tretinoin or isotretinoin in gel form (0.05% to 0.1%), are generally similar to those obtained with systemic retinoid [20].

**Bleomycin**

Bleomycin, a cytotoxic antibiotic, is an alternative treatment of oral leukoplakia. It is taken for squamous cell carcinoma of the head and neck region, oesophagus, and skin [14]. The use of topical 1% bleomycin applied once daily resolved oral leukoplakia in 14 days [21]. It is not very often used in practice for its adverse effects (mucocutaneous reactions, which include stomatitis, alopecia, pruritic erythema, and vesiculation of the skin) [14].

**Photodynamic therapy**

Photodynamic therapy is a noninvasive method of treatment for head and neck tumors [22]. It is based on photochemical reaction, initiated by light activation of a photosensitizing drug causing tumor cell death. It requires the simultaneous presence of a photosensitizing drug (photosensitize), oxygen, and visible light and it is a non-thermal reaction [23]. The photosensitize (aminolevulinic acid-ALA) is administered systemically by intravenous injection or can be topically applied. After a short time it is collected in the target tissue and it is activated exposure to low-power visible light of a drug-specific wavelength. The result will be some reactive oxygen species which will induce damage to cell components (structural proteins, enzymes, DNA, and phospholipids). The important structures of the organ
are maintained with good functional and cosmetic outcome [23]. There are several photosensitizers which have been developed and approved in time: (1) photofarin has been approved in many countries for the treatment of esophagus cancer and lung cancer; (2) 5-Aminolaevulinic acid was also approved in several countries for the treatment of skin cancer; (3) verteporfin for the treatment of macular degeneration (4) foscarn is the only photosensitize that has been approved for the treatment of advanced squamous cell carcinoma of the head and neck in Europe in the year 2001 [23]. There are several studies [14,24,25] which reported the use of 5-Aminolaevulinic acid in the treatment of oral leukoplakia with good results and no recidives for 9 months follow-up.

Elimination of risk factors

The ceasing of tobacco use is a prior action in case of tobacco associated leukoplakia. There are no studies on groups of smokers to assess the malignant transformation. But encouraging patient to stop smoking will reduce the incidence of leukoplakia and can even resolve a large number of lesions [5,26].

Wait and see attitude

A possibility of treatment is a strict clinical and histological surveillance. This involves with frequent clinic visits and biopsies (of suspected lesions), but without active intervention. This form of treatment is intended to diagnose a malignant transformation as soon as possible, thus giving the best possible prognosis [7]. In present there are studies suggesting that the natural history of leukoplakia might be independent from the treatment and there are some lesions destined to malignant transformation regardless of the therapy adopted [7].

Conclusions

The degree of epithelial dysplasia is mandatory for the correct choice of the treatment. In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended [7]. Mild dysplasia or the absence of dysplasia can be completely removed or not. In this case the decision should consider clinical factors such as location, size and the patient's engagement in smoking cessation [27].

Acknowledgement: This paper is supported by the Sectorial Operational Programme Human Resources Development (SOP HRD) 2007-2013, financed from the European Social Fund and by the Romanian Government under the contract number POSDRU/1071/1.5/S/82839.

Bibliography


