Cryosurgery with refrigerant gas as a therapeutic option for the treatment of leukoplakia: a case report

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Leukoplakia is a nondetachable, potentially malignant, white lesion that is commonly found in smokers of advanced age. Leukoplakia occurs more frequently in men; however, there is a higher index of dysplastic changes and malignant transformation in women. The proposed treatments for this disease range from monitoring to surgical excision. Cryosurgery has been reported as an alternative to conventional surgery. Cryosurgery destroys the tissues of a potentially malignant lesion through the application of low temperatures. This technique offers a low rate of postsurgical infection, absence of hemorrhage, and ease of application, and it is widely accepted by patients. The most commonly used cryogenic agent, liquid nitrogen, is costly and difficult to use. The objective of this article is to suggest the use of a combination of refrigerant gases (propane and butane), commonly employed in pulp sensitivity tests, for cryosurgery of potentially malignant lesions of the oral cavity and to report a case of leukoplakia treated with this approach.

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Malignant lesions of the oral cavity represent 3% of all malignant neoplasms.[1] Like many carcinomas, squamous cells in the mouth develop from potentially malignant lesions (PMLs). The correct diagnosis of these lesions and their appropriate management are important targets for cancer prevention.[1-3]

Leukoplakia is considered a PML, and the diagnosis is essentially clinical. This lesion presents as a white patch that is not detachable and is not classified as any other pathologic condition. Leukoplakia is found in 0.2%-3.6% of the population and has a predilection for middle-aged and elderly men.[1-3] Although leukoplakia occurs more frequently in men, there is a higher index of dysplastic changes and malignant transformation in women.[3]

The etiologic agents related to the pathogenesis of leukoplakia include smoking, alcohol, and candidiasis.[1-3] Other authors have proposed herpes simplex virus and human papillomaviruses (HPV-16 and HPV-18) as possible pathogenic sources.[2-4] Smokers have a significantly increased risk of leukoplakia. Studies have shown that 80% of these lesions are diagnosed in patients who smoke.[2-4] The isolated use of alcohol is not described as an increased risk factor for development of leukoplakia; however, consumption of alcohol is well known for a synergistic action with smoking in relation to leukoplakia and oral cancers. A curious fact is that evidence has shown that oral leukoplakia has a greater probability of malignant transformation in nonsmokers than in smokers.[2-4] The presence of HPV-16 is also associated with a higher rate of malignant transformation.[2-4]

The initial treatment of leukoplakia consists of removal of dental irritants, such as dental prostheses, and behavior modifications such as cessation of alcohol consumption or smoking. When there is no significant dysplastic change, periodic monitoring can be considered as an option.[2,5] When histopathologic analysis reveals either moderate or severe dysplasia, complete surgical removal of the lesion is required. This is achieved through conventional excision, electrocauterization, cryosurgery, or laser ablation.[2,5]

Cryosurgery is a therapeutic modality that causes cell destruction by the localized application of low temperatures. The application of refrigerant gases in living tissue causes the destruction of the tissue in a few minutes. This mechanism is beneficial when used against pathologic tissues. Since it is effective, simple, and easy to apply, this method has been widely employed in the treatment of skin lesions as well as in the dental area. There are major advantages in using this technique, such as patient acceptance, absence of transoperative hemorrhage, and a low rate of postsurgical infection.[6-8]

Fig 1. Initial clinical aspect. The white lesion on the dorsum of the tongue is about 2 cm in its greatest diameter.

Fig 2. Appearance after the first session of cryosurgery. The area presents hyperemia.

Cryosurgery directly affects the tissue due to freezing. Freezing causes cell disruption, cellular dehydration, electrolyte disturbances, enzyme inhibition, and modification of proteins. These cumulative effects cause irreversible damage to the cellular metabolism, which leaves the cell vulnerable. This process is followed by a thawing phase, with a sudden entry of water to the cell interior, causing damage to the cell membrane. In addition, the thermal shock of increasing temperatures also causes damage to the cell membrane. Gage et al demonstrated—both in vitro and in vivo—that cryosurgery causes necrosis in cells from the center of a lesion and that the periphery of the lesion undergoes apoptosis approximately 12 hours postfreezing.[9]

The indirect negative effects of cryosurgery are also important to consider. These may be caused by vasoconstriction and vascular stasis during cold weather, which, after normalization of the blood flow, may lead to the formation of edema. Side effects of cryosurgery may also include cardiac tamponade with consequent thrombi, ischemia, and hypoxia, resulting in a change in cellular pH and eventual cell death.[9]

The thawing cycle is as important as the freezing cycle. Both phases have their importance for an effective result of cryosurgery. Freezing should happen quickly, while thawing preferably should occur slowly, enabling the creation of a liquid medium that is favorable to intracellular protein denaturation reactions. Another factor to be taken into consideration is the repetition of this process. The multiple cycles used during cryosurgery may lead to deleterious changes and consequent increased tissue damage.[9-11]

The cryogenic agents suggested for the treatment of lesions are liquid nitrogen, tetrafluoroethane, hydrofluorocarbons, and associations of ethane and butane gases, dimethyl ether–propane, and propane-butane.[8,12,13] These systems are used in open or closed forms.

The objective of the present article is to describe a case of leukoplakia on the tongue treated through cryosurgery with a combination refrigerant gas (propane and butane).

Case report

A 65-year-old woman presented at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, University of Pernambuco, Camaragibe, Brazil, complaining about an asymptomatic white patch on her tongue. The patient stated that the patch first appeared 2 years ago; the patient's history did not reveal any comorbidities. The extraoral physical examination showed no change in the cervical lymph nodes, while the intraoral examination found a white patch on the upper surface of the tongue, measuring approximately 2 cm in diameter (Fig 1). Scraping showed the lesion to be nondetachable. The patient's current use of a prosthesis was determined to be a possible irritant.

The incisional biopsy for confirmation of the hypothesis that was formulated in view of the clinical findings found, as expected, a layer of hyperparakeratosis and mild epithelial dysplasia, consistent with a clinical diagnosis of leukoplakia. The proposed treatment for the patient was cryosurgery.

After administration of local anesthesia, cryosurgery was performed after both intraoral (chlorhexidine gluconate 0.12%) and extraoral (chlorhexidine gluconate 2%) antiseptics were applied to the surgical area. For patient comfort, an anesthetic block was initiated at the lingual nerve (mepivacaine 2% with epinephrine 1:100,000).

The cryogenic agent used was a combination of propane and butane gases (Roeko Endo-Frost, Coltène/Whaledent, Inc). First the lesion area was dried with suction and isolated with gauze up to the area of leukoplakia. Endo-Frost was then applied to the area through the delivery tube in 2 sessions, using high-powered suction to minimize the gas dispersion in the oral cavity (Fig 2). Each session consisted of two 1-minute cycles with an interval of 2 minutes between cycles. The second session took place 7 days after the first (Fig 3).

The patient reported pain during the postoperative period, which was easily controlled with analgesics. After the healing period, the area presented with color and appeared normal. This result was confirmed by incisional biopsy. The patient's follow-up at 1 year posttreatment showed no signs of complications or recurrence (Fig 4).

Discussion

PMLs are characterized by a change in the morphology of benign tissue and a greater than normal risk of malignant transformation.[1] Examples of PMLs are leukoplakia, erythroplakia

Fig 3. Appearance 7 days postoperatively. The tongue is in the process of healing without signs of infection.

Fig 4. Final clinical aspect. At the 1-year post-treatment follow-up, there are no signs of recurrence or complications.

(usually red in appearance), and erythroleukoplakia (red, or sometimes white and red, in appearance). PMLs have been associated with malnutrition, lupus erythematosus, vitamin deficiencies (A, B, and C), immunosuppressive diseases (AIDS), and syphilis.[1]

Leukoplakia is by far the most common clinical presentation of PMLs. The differential diagnosis involves ruling out other white lesions found in the oral cavity: lichen planus, verruca vulgaris, burns, white sponge nevus, leukoedema, and chronic biting of the buccal mucosa. Leukoplakia lesions can be classified according to their clinical presentation as well as the extent and degree of dysplasia. Leukoplakia may present as a thin, flat, smooth, and translucent lesion, which has a very low potential for malignancy; as a thick, homogenous lesion, with a 1%-7% chance of malignancy; as a granular or verruciform lesion, with a 4%-15% chance of malignancy; or as a veined or erythroleukoplakia lesion, with an 18%-47% chance of malignancy.[2,5] PMLs that are nonhomogenous have a greater opportunity to present dysplastic changes.[2,5]

Histopathologically, leukoplakia presents sometimes as hyperorthokeratosis (a granular cell layer with missing nuclei) or, more rarely, as hyperparakeratosis (a thickened keratin layer with nuclei). These dysplasias are present in 3%-25% of leukoplakia cases.[1,5] Abnormalities in the proliferation, maturation, and differentiation of epithelial cells in leukoplakia lesions are graded as mild, moderate, or severe. The risk of malignant transformation is compatible with the degree of change of dysplastic epithelium and is probably due to the progressive accumulation of genetic changes over time. In the presence of dysplasia, there is normally a dysregulation of the activity of the p53 protein and consequently uncontrolled proliferation.[1,5]

In a follow-up study of 144 patients with leukoplakia, Brouns et al found that the potential for malignant transformation was 11%.[3] However, the only data that offered clinically significant value for the possibility of malignant transformation was the size of the lesion (larger than 4 cm). The malignant transformations occurred on average over a period of approximately 5 years, with female predominance in a ratio of 3.7:1.[3] The literature is not clear about why female patients have a greater risk of malignancy associated with leukoplakia; more research is needed on this subject.

Conservative treatment of leukoplakia involves the elimination of sharp tooth edges and incorrectly adjusted prostheses that can cause ongoing trauma; suppression of outbreaks of infection; change in habits concerning the use of tobacco and alcohol; and avoidance of hot or spicy foods. Vitamin supplements (A, B, C, and E) may be helpful, and administration of retinoids, lycopenes, β-carotene, topical antifungal agents, bleomycin, and photodynamic therapy can be considered. The absence of results within 3 months of conservative treatment indicates a need for surgery. It has been reported that the rate of recurrence is higher after conservative management than it is in cases treated surgically.[2,5]

The first reports on the use of cold as a medical therapy date back to approximately 4000 BCE.[3,5,7] The ancient Egyptians understood the power of low temperatures in the treatment of inflammation. Hippocrates reported the use of low-temperature therapy in 460 BCE. Cryosurgery has been used in dentistry for more than 30 years to treat various oral pathoses, such as leukoplakia, submucosal fibrosis, pyogenic granuloma, actinic cheilitis, vascular lesions, mucoceles, keratoacanthoma, and papillomatous hyperplasia of the palate.[3,5,7]

This method of treatment offers several advantages: low cost, technical ease, effectiveness, minimal pain, absence of bleeding, low rate of postoperative infections, and esthetic results. Cryosurgery is ideal for high-risk patients, including those with coagulopathies and elderly individuals with systemic complications. It is also ideal for extensive lesions, lesions in areas of difficult surgical access, and lesions in areas where esthetics is important. Another important factor is the biocompatibility offered by this treatment modality. Studies of toxicology have confirmed the absence of oncogenic or genotoxic effects after cryosurgery.[3,5,7] In the present case, the advantages of this method of treatment were verified by the minimal postoperative discomfort reported and the excellent results observed at follow-up.

Cryosurgery is a relatively painless procedure due to the immediate blockade of neural transmission in the affected area resulting from the local anesthetic effect produced by low temperatures. When compared to conventional surgery, cryosurgery is well tolerated as a therapeutic option for patients.[14] Patients have been reported to be both tranquil and comfortable during therapeutic application of refrigerant gases.[14]

The cryogenic agent used most often for the treatment of lesions of the oral cavity has been liquid nitrogen, which is considered the gold standard for cryosurgery. In spite of its effectiveness and low cost, liquid nitrogen requires a costly apparatus (container and cryocautery probes) that has a short shelf life and is considered difficult to operate.[6,8,9,15] Its use by the clinician in the office is, in most cases, impossible. According to the literature, many other cryogenic agents are more accessible.[6,8,9,15] Among these cryogenic agents are refrigerants. A mixture of propane and butane gases has been widely used in daily dental practice in pulp sensitivity tests.[6,8,9,15]

According to the manufacturer of Endo-Frost and other authors, the mixture of propane and butane gases can reach –50°C.[7,8,16-18] A study by Zacarian et al postulated that the minimum effective temperature range for treatment of lesions in soft tissues is between –20°C and –30°C.[16] Thus, the use of Endo-Frost to perform cryosurgery is effective because it reaches temperatures even colder than this level. This range is now indicated in the treatment of various oral and cutaneous diseases.[7,8,16,17] The use of propane-butane refrigerants has become increasingly common in dental surgery, as it is an effective treatment with no signs of recurrence or complications.

Conclusion

Early diagnosis is the key to better results in the treatment of leukoplakia. Leukoplakia occurs more frequently in men; however, there is a higher index of dysplastic changes and malignant transformation in women. This fact must be considered in the management of these patients. Detection, early treatment, and monitoring are the main keys to preventing PMLs from becoming malignant. The use of cryosurgery with propane-butane gas, as reported in this article, is an effective and safe alternative therapy that the dentist can apply for the management of leukoplakia.

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