

Oral proliferative verrucous leukoplakia treated with the photodynamic therapy: a case report

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Summary

Aims. About 60% of the oral cancer arise on a pre-existent potentially malignant disorder of oral mucosa like the oral proliferative verrucous leukoplakia. The treatment with the photodynamic therapy of these lesions represents, in the last years, an innovative, non-invasive and effective therapeutic possibility to achieve the secondary prevention of oral cancer. In the last decade, case reports have described patients with similar treated through a photochemical reaction induced by laser light. The aim of this study is to evaluate the effectiveness of the topical 5-ALA photodynamic therapy in the treatment of a case of Oral proliferative verrucous leukoplakia.

Case report. A female patient of 80 years old affected by white verrucous plaques on the right buccal mucosa was recruited for our case report. The right side lesion was treated with the photodynamic therapy with topical administered 5-aminolevulinic acid using the 635 nm laser light to activate the photosensitizer.

Results. The lesion showed complete response after 4 sessions of photodynamic therapy and no recurrence was noticed after 12 months.

Conclusions. The photodynamic therapy can be considered an effective treatment in the management of oral verrucous proliferative leukoplakia,

but more clinical trials, with prolonged follow-up controls, are necessary to evaluate its effectiveness in the mid and long time period.

Key words: photodynamic therapy, oral leukoplakia, oral cancer, 5-aminolevulinic acid, potentially malignant disorders.

Introduction

Oral squamous cell carcinoma (OSCC) is the fifth common cancer in the world with an annual worldwide incidence exceeding 300,000 cases (1). The disease is an important cause of death and morbidity, with a 5-year survival less than 50% (2). These poor data are mainly due to the frequent great diagnostic delay that characterizes the early phases of OSCC cases. So the prevention of OSCC is the most important approach to minimize its incidence and to provide a better quality of life of patients. In particular, the secondary prevention is based on the early diagnosis and management of the so-called Potentially Malignant Disorders (PMDs), a series of pathologies characterized by the risk of neoplastic degeneration (2). Among the PMDs of the oral mucosa the most frequent is the Oral Leukoplakia (OL) (2). Clinically, OLs can be classified in two different groups: homogeneous and non-homogeneous lesions. Moreover, another type of OL characterized by a multifocal localization and a very high risk of malignant transformation (about 70%) is the oral proliferative verrucous leukoplakia (OPVL) (3,4). The OPVL is more common in middle-aged women and the female-to-male ratio is 4:1 (5); is of uncertain etiology and is not strongly associated with tobacco use or alcohol with the HPV infection that may play an important role in these lesions (5). Multiple oral sites may be involved and before malignant transformations can pass many years up to even some decades (4).

In the last decades many treatments were used in the treatment of PMDs: traditional surgery (6), electro-surgery, cryosurgery, laser surgery and the administration of drugs (e.g. carotenoids, exc.) (7). Recently the progresses in the knowledge suggested the possibilities of a non invasive treatment of OL with the laser (8). Generally the laser interaction on oral mucosa is based on the photothermic effect, that means to have the possibility to cut the tissue to perform a biopsy (9,10). Another effect of laser on soft tissue is a photochemical effect, the so called photodynamic therapy (PDT) that is based upon a photochemical laser light induced reaction, strictly directed on patho-

logic cells, permitting a safe and complete removal of the lesion without sacrifice of healthy tissue (11). The PDT involves three components: light, a photosensitizer and oxygen. A photosensitizer, or its metabolic precursor, is locally applied upon the lesion. The activation of the photosensitizer with a low level laser light, determines the transition of the agent from a low energy ground state to an excited singlet state. The singlet state can react with endogenous oxygen to produce singlet oxygen and other reactive oxygen species (ROS), causing a rapid and selective destruction of the target tissue (Fig. 1).

These photochemical induced reactions lead in many ways to the destruction of neoplastic tissues; as a first, ROS kill directly tumor cells; in other cases, PDT damages the tumor associated vascular tissues, leading to thrombus formation and subsequent tumor infarction. Moreover PDT can also elicit an immune response against tumor cells (12). The advantages of the PDT in the treatment of OL were confirmed in many studies in literature (8, 12-14). On the other hand, PDT in several cases, requires multiple sessions of irradiation to achieve complete regression of the lesion and the costs of the laser and of the photosensitizers are high.

A lot of natural and synthetic agents have photosensitizing potential, but the 5-aminolevulinic acid (5-ALA) is one of the most important photosensitizer in the management of OL. For the treatment of pre-malignant and malignant lesions in the oral cavity has been used PDT with topical administered 5-ALA. Due to the limited depth of topical 5-ALA administration, and the limited light penetration of 635 nm laser light, the use of 5-ALA is restricted to superficial lesions (1-2 mm) such as homogeneous flat leukoplakia, erytroleukoplakia and verrucous leukoplakia (15). 5-ALA is rapidly cleared from the tissue and the body within 48 hours and skin photosensitivity lasts less than 24 hours (15). The aim of this study is to report the management of a clinical case of OVPL through the PDT obtained with the locally administration of a 20% gel of 5-ALA.

Case report

A female patient of 80 years was recruited for the study; history and general physical investigation revealed no relevant findings and no tobacco-chewing or smoking habit was reported from the patient. The clinical examination of the mouth revealed painless white verrucous plaque lesion with multiple peaks on the buccal mucosa bilaterally (Fig. 1). A clinical provisional diagnosis of OVPL was made considering the multifocal, verrucous aspect of the lesion (16) and, subsequently, this diagnosis was confirmed by incisional biopsy of the diseased mucosa. The histological examination revealed proliferative corrugated hyperkeratosis, acanthosis, mitoses, broad rete ridges and inflammatory cell infiltrated on the connective tissue. The lesion was photographed for further evaluation. Considering the dimension of the lesion, we de-

cidated to treat the lesion with a minimal invasive technique: the topical 5-ALA-PDT. The consensus for the treatment from the patient was required before the start of the therapy.

The formulation of 20% gel of 5-ALA used in our study was prepared using 25% of Lutrol F127 (BASF Chemtrade GmbH, Burgbernheim, Deutschland) and 1% of Carbopol 971P (Lubrizol, Cleveland-Ohio State, USA). Double concentrated gels of Lutrol F127 and Carbopol 971P in water were separately prepared prior to mixing. After refrigerating at 4° C, the solution of Lutrol F127 was mixed with equal volume of the Carbopol 971P gel and the mixture was stored at 4° C. Prior to use, 800 mg of gel was mixed with 200 mg of 5-ALA (Fagron GmbH, Barsbittel, Deutschland). The formulation was used within 3 hours after the preparation. A thin layer of gel was applied topically on the lesion using a microbrush (Fig. 2). For the first 10 minutes after the application of the gel, three cotton rolls were placed onto the orifices of major salivary glands to avoid the dilution of gel by the saliva. In addition, during this period, the doctor controlled the salivary flow by intermittent suction. The gel was left 1.5 hours over the lesion to permit its gathering into target cells. During this period, a gauze was placed over the lesion to avoid the removal of gel. For the activation of the photosensitizer



Figure 1. Clinical aspect of the lesion before 5-ALA-PDT treatment.



Figure 2. Application of 20% 5-ALA gel on the lesion.

was used a diode laser of 635nm (Doctor Smile-Dental Laser, Vicenza, Italy) (Fig. 3). Each application consisted of five 3 mins and one 100s irradiations with five 3-minutes breaks for a total of 1000s (fluence rate: 100mW/cm², total energy dose 100J/cm²) using the fractionated protocol of irradiation described by Chen et al. (14). With this irradiation protocol, the lesional epithelial cells have the possibility to regenerate new PpIX and obtain new oxygen during multiple 3-minutes resting period. The laser has been set at a very low power (100mW), to take advantage only of the photochemical effect of the laser, without the overheating of the targeted tissues. The treatment was performed twice a week until the clinical resolution of the lesion. At the end of the therapy, the patient was arranged for a follow-up schedule once a month and clinical photographs were taken at each patient's visit to evaluate the clinical outcome of PDT. The lesion showed complete response after 4 treatments of PDT (Fig. 4). The treatment was painless and the patient did not require either local anesthesia during the irradiation or analgesics drugs after the treatment. The examination at 6 months after the last session of PDT showed that the OPVL disappeared completely with a good healing of the mucosa. The patient was satisfactory for the treatment and the follow-up at 12 months showed no recurrence (Fig. 5).



Figure 3. Irradiation with 635 nm diode laser.



Figure 4. Clinical resolution after 4 treatments of 5-ALA-PDT.



Figure 5. Clinical aspect after 12 months of follow-up.

Discussion

In our case the results are encouraging. The successful clinical outcome could be due to the gel preparation, the fractionated protocol of irradiation used, and the characteristics morphological, histologic and biological features of the lesion. The 20% 5-ALA gel was adherent to oral mucosa and partially resistant to the dilution of saliva. This aspect is very important because the gel form helped the absorption of 5-ALA from the mucosal surface. The fractionated protocol of irradiation allows the regeneration of new PpIX by the lesional epithelial cells and the obtaining of new oxygen during multiple 3-minutes rests. So results in a more successful clinical outcome for the therapy of OVPL. Moreover the verrucous appearance of this lesion provided a large area of retention for the gel, resulting in a difficult removal of 5-ALA from salivary flow.

One of the main limitation of the 5-ALA-PDT is the low depth of penetration of the topical photosensitizer. For this reason, this therapy is restricted to superficial lesions of 1-2 mm of thickness.

Previous study demonstrated the effectiveness of this therapy in the management of OL. Fan et al. (13) treated 12 patients with oral dysplastic lesions using orally administered ALA. All 12 patients showed regression of the lesion of the lesions to normal or less dysplastic. Kübler et al. (13) treated 12 patients affected by leukoplakia of the oral mucosa for several years. 20% ALA cream was applied to the lesion for 2 hours. Five patients showed complete response, four patients showed a partial response, and in three patients treatment showed no response. Sieron et al. (14) treated 12 patients with lesions that affected a variety of intraoral sites using 10% ALA cream. Irradiation was performed in 6-8 sessions of therapy. A complete response was obtained in 10 patients, with one recurrence during 6 months. The potential advantages of the PDT for treating the OPVL are: moderate side-effects, possibility to give repeated doses without cumulative toxic effects, excellent aesthetic results with healing process characterized by little or no scars and re-

duction of pain during the treatment. The poor side effects and the lack of invasiveness permit the repetition of the treatment in case of recurrences even in the short period. The disadvantages of the PDT consist mainly in its high costs and the longer duration, up to five weeks.

Conclusions

In this case report, 5-ALA-PDT has been an effective and non-invasive treatment for the management of the OVPL. It has been easily accepted by the patient. The main problem of this therapy is the difficulty to avoid the removal of gel by salivary flow. The development of gel or other vehicles more adhesive to oral mucosa may enhance the absorption of the photosensitizer increasing the success of clinical outcome of PDT. In spite of the encouraging results of our study, more clinical trials with prolonged follow-up controls are necessary to evaluate the real absolute effectiveness of this therapy in the mid and long time.

List of abbreviations

OSCC, Oral squamous cell carcinoma; PMD, Potentially Malignant Disorder; OL, Oral leukoplakia; OPVL, Oral proliferative verrucous leukoplakia; PDT, Photodynamic therapy; 5-ALA, 5-aminolevulinic acid; PpIX, Protoporphyrin IX; OVH, Oral verrucous hyperplasia; OEL, Oral eythroleukoplakia.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The study has been conducted in accordance with the Declaration of Helsinki.

Conflicts of interest

The authors declare that they have no competing interests.

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