Actinic Cheilitis Treated with Photodynamic Therapy: Case Report of an Innovative Successful Therapy

Francisca Reculé[1,*], María Teresa Barroilhet[2], Maximiliano Curi[3], Marianne Kolbach[4] and Sergio González[5]

[1]*Medical Physician, Internal Medicine Department, Hospital de Carabineros, Santiago, Chile*

[2]*Medicine Student, Los Andes University, Santiago, Chile*

[3]*Dermatology Resident, Pontificia Universidad Católica de Chile*

[4]*Asistent Professor, Dermatology Department, Pontificia Universidad Católica de Chile*

[5]*Asistent Professor, Histopathology Department, Pontificia Universidad Católica de Chile*

Abstract: Actinic cheilitis (AC) is a chronic inflammatory disease, considered the main precancerous lesion of the lip, due to it antecedents squamous cell carcinoma (SCC). AC pathogenesis is related to ultraviolet radiation (UVR) chronic exposure with persistent elastosis, but genetic predisposition also has been proved. Multiple therapies have been used with moderate success, being recently proposed photodynamic therapy (PDT). We want to report a case which although is not rare; it was treated with an innovative therapy (PDT). A 28-year-old male consulted for a 9-month evolution history characterized by recurrent lip dryness, ulcers and fissures. At the physical exam an erythematous plaque with hyperkeratotic edge of the lower lip was observed. Histological study revealed an AC with moderate dysplasia. Two sessions of PDT with methyl aminolevulinate (METVIX) and red light were performed, with excellent clinical and histological response. Control biopsy demonstrated non-dysplastic AC. We propose that PDT is a new and effective non-invasive available option for treatment of AC.

Keywords: Actinic cheilitis, photodynamic therapy, metvix, adult, lip.

INTRODUCTION

Actinic cheilitis (AC) is a chronic inflammatory disease, considered the main precancerous lesion of the lip, preceding squamous cell carcinoma (SCC). Its pathogenesis is related to chronic exposure to ultraviolet radiation (UVR), with clear genetic predisposition [1, 2]. Generally it presents at fourth and fifth decades of life, although it can appear at any age. It is more common in men, up to 3 times [2, 3], and 95% is located in the lower lip [4]. With higher incidence at tropical climates, particularly in low photo type individuals who work outdoor [1]. AC is the lip analogous for cutaneous actinic keratosis (AK), but represents a higher risk of progression to SCC, with relative risk of 2.5 [2], ranging between 1.4% and 36% of 1 to 30 years, with no consensus on this matter [4].

Clinically AC presents as persistent squamous and rugged injury, with long-standing labial dryness, refractory to use of lip balms. On physical examination keratosis, fissures, erythema, impaired color and pathognomonic blurring edge of the lip (vermilion atrophy) may be observed, associated or non-associated to focused ulceration. The lesion may be more thickened as it progresses. Leukoplakia is also very important because constitutes the most common change predating SCC [4]. Leukoplakia or idiopathic white patch normally refers to a condition where areas of keratosis appear as firmly attached white persistent patches on the mucous membranes of oral cavity and that cannot be characterized as any other definable lesion [5].

Histopathology makes the definitive diagnosis, ranging from isolated hyperkeratosis to SCC [1]. Epithelial dysplasia, hyperkeratosis or parakeratosis, acanthosis and areas of atrophy may be observed. Solar elastosis is also very common. In dermis, inflammatory infiltrate may be found, mainly composed of lymphocytes [3]. The progression from AC to SCC is very important to establish because leads the therapy, and because its morbidity implications, due to it carries a heavy prognosis, particularly if diagnosed late. Lip SCC constitutes 40% of head and neck carcinomas [6], and 90% of oral cavity cancers. At this location SCC has up to 4 times early metastases to regional lymph nodes [2]. with survival ranging from 62 to 79%, stressing out the importance of early detection and treatment of pre-malignant lesions [2].

Multiple therapies have been used to treat AC with moderate success, being increasingly used photodynamic therapy (PDT), due to its effectiveness, lack of long-term recurrence, low rate of adverse effect

*Address of correspondence to this author at the Av. Vicuña Mackenna 4686, Macul, Santiago, Chile; Tel: +56950000050; E-mail: f.recule.g@gmail.com

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and excellent cosmetic results [2, 7]. It includes a photosensitizer, which induces targeted apoptosis and consequent destruction of dysplastic tissue, being very selective. Targeted apoptosis meaning directed cell death due to a specific therapy. Inhibition of angiogenesis and impairment of vascular functions after PDT is frequently associated with the tumor remission and is considered one of the main antineoplastic PDT effects [8]. Metvix is a topical photosensitizer composed by 16% of methyl aminolevulinate, indicated in AK, superficial basal cell carcinoma, and recently for AC [9].

We report a case of AC with moderate dysplasia, treated with PDT with topical Metvix, with excellent clinical and histological results.

CASE REPORT

A 28-year-old non-smoking and healthy male patient, with chronic exposure to sunlight labor from childhood, consulted for lip dryness, ulcers and fissures of 9 months of evolution. No history of tumor or bleeding. No family history of skin cancer. On physical examination, an erythematous plaque with hyperkeratotic edge, eroded, cracked and crusty on the lower lip (Figure **1**) with the undamaged mucosa without leukoplakia or other lesions observed. AC was proposed as diagnostic hypothesis, histological study was requested, and an incisional biopsy of the lesion was performed. Biopsy results were reported as ulcerated AC with moderate dysplasia, with signs of atrophy and inflammation (Figure **2**). UVB radiation causes most damage, altering gene transcription to mRNA and preventing DNA replication, reducing this way the mitotic activity, and subsequently generating atrophy of epithelium, and therefore a decline in photo-protective capacity. The patient was summited to two sessions of PDT with Metvix and red light separated by one month, with excellent clinical response (Figure **3**). Control biopsy showed AC with no dysplasia (Figure **4**).

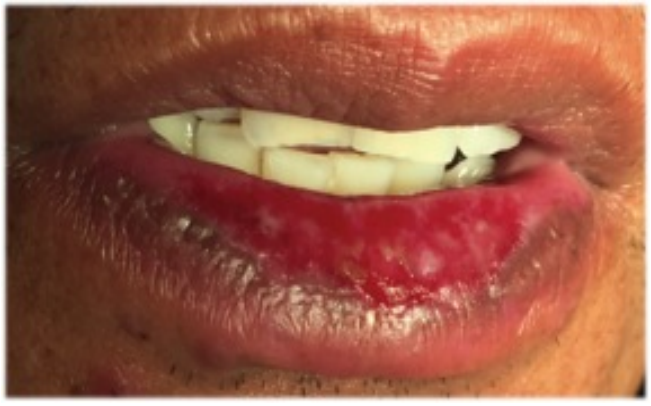

Figure 1: In this picture we can apreciate the squamous rugged lesion of the lower lip.

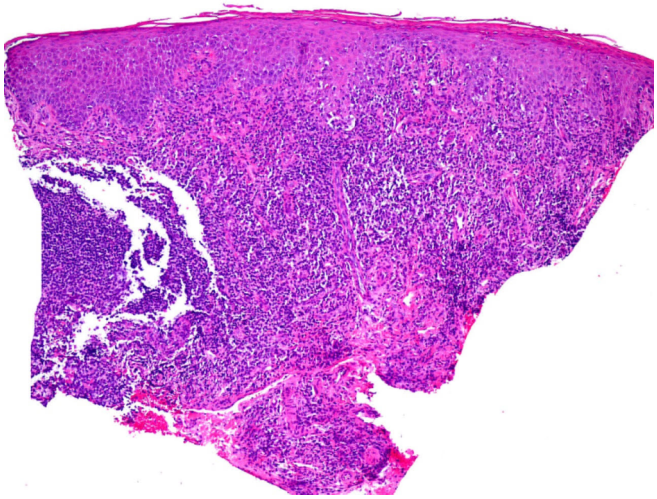

Figure 2: Histopathologic picture of biopsy lesion with hematoxilin eosine technique with significant tissue displasia.

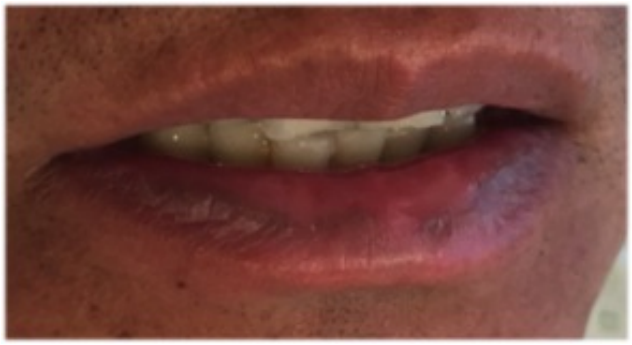

Figure 3: Clinical picture post treatment with photodynamic therapy, with resolution of lip dryness.

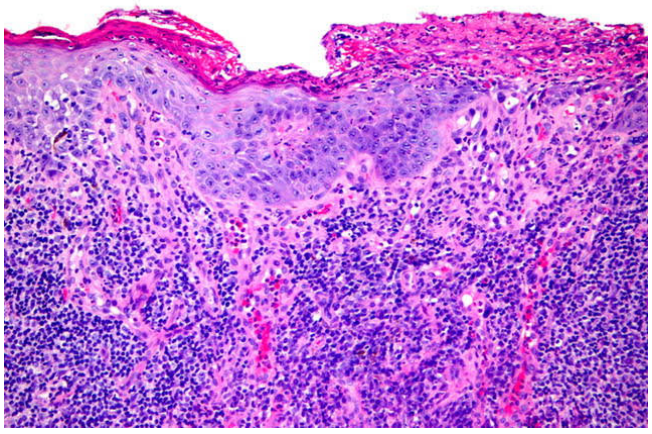

Figure 4: Histopathologic picture of biopsy lesion with hematoxilin eosine technique post treatment with resolution of tissue displasia.

DISCUSSION

AC has a high morbidity rate due it precedes SCC [4, 6]. Progression is regulated by tumor suppressor genes, chemokine and regulatory proteins of cell proliferation, which play a vital role in its biological behavior. Among them, stands out the role of p53 protein regulating the cell cycle and tumor suppressor, along with the oncogene c-bcl-2, playing a fundamental role in the development of actinic lesions [4]. Risk factors of progression include male, low photo-type, immunosuppression (post-transplant or patients infected with the human-immunodeficiency-virus), advanced age, and smoking [10]. Our patient was photo-type IV, didn´t smoke, but had chronic sun-exposure. There are also genetic predisposition such as xeroderma pigmentosum, porphyria cutanea tarda and oculocutaneous albinism [11], none of these were present in our patient.

Histologically, labial epithelium has thinner stratum corneum and fewer melanocytes in dermo-epidermal junction, making it more vulnerable to genetic and molecular damage caused by UVR. UVB radiation causes most damage, altering gene transcription to mRNA and preventing DNA replication, reducing mitotic activity, and subsequently generating atrophy of epithelium, and therefore a decline in photo-protective capacity. This occurs concomitantly with ionizing radiation damage with consequent formation of free radicals. The knowledge of tumor markers and prognostic factors has positive impact on patient follow-up and may be treatment targets for future research.

A very important clue is that AC may be clinically indistinguishable from SCC, although there are some clinical signs that may guide the dermatologist [1-4].

Signs of progression from AC to SCC are: persistent injury for more than two weeks, texture changes, effacement of the lip vermilion, atrophy, nodularity, ulceration or bleeding, independent of the time of evolution; [4] making the biopsy mandatory in these cases [2].

At histopathology atypical keratinocytes are the most relevant finding, gradually settling in epithelium, ranging epithelial dysplasia, as mild, moderate or severe (carcinoma in situ), and its severity is related to the development of invasive carcinoma [4, 6].

The SCC is the deadliest non-melanoma skin cancer, so that early treatment of AC is the most effective way to prevent it.

Treatment of AC aims to remove or destroy dysplastic epithelium. Multiple therapies have been used successfully such as: vermilionectomy, cryotherapy, topical chemotherapy with 5-fluorouracil or trichloroacetic acid, electro cauterization, immunomodulators (as imiquimod), laser ablation with carbon dioxide, YAG laser and PDT [2, 4], which with the proper spectrum of visible light converts oxygen into cytotoxic oxygen reactive species that alter the cellular structure of the target tissue, being extremely specific. Vermilionectomy is indicated mainly in AC with severe dysplasia and SCC [4]. Surgical treatments have significant adverse effects, mainly homeostatic (bleeding and bruising), but also cosmetic (scars), while nonsurgical treatments have an uncertain efficacy [4], but later PDT has proven itself superior long term efficacy in the treatment of AK when compared with other conventional treatments, like cryotherapy [7]. There are randomized trials and systematic reviews that evidence the effectiveness of PDT in AC, whose conclusion stated that it is a safe therapy, being able to treat the lesion clinically and histopathologically, proving to be an excellent tool for its treatment [2, 7].

There have been great advances regarding molecular pathogenesis of AC, emerging new therapeutic proposals, like PDT, which has demonstrated to be an effective treatment of neoplastic precursor lesions, such as AC.

CONFLICT OF INTEREST

We declare to have no conflict of interest.

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