UNIVERSIDAD DE CUENCA

Facultad de Odontología

Carrera de Odontología

Actinic cheilitis: clinical, pathological and therapeutic considerations.

Artículo académico previo a la obtención del título de Odontólogo

Autores:

María Paz Pinos Gavilanes

CI: 0106568868

Correo electrónico: pazpinosgavilanes@gmail.com

DDS. Daniel Esteban Pinos Gavilanes

CI: 0105536031

Correo electrónico: drdanielpinosg@gmail.com

Tutor:

DDS. MSc. PhD. Diego Mauricio Bravo-Calderón

CI: 0104514237

Cuenca, Ecuador

01-junio-2021

Actinic cheilitis: clinical, pathological and therapeutic considerations.

Abstract: Actinic cheilitis (AC) is a chronic inflammation that affects more frequently to the lower lip and is considered as a potentially malignant disorder that could develop into squamous cell carcinoma (SCC). AC is caused by excessive exposure to ultraviolet (UV) radiation, mainly sunlight radiation. Fair-skinned male patients, older than 50 years, who have worked outdoors or have had long-term sunlight exposure are more susceptible to develop this lesion. Their clinical manifestations are very varied; nevertheless, they are not related to the histopathological alterations that can be found. Histopathological diagnosis is the most important predictive factor of malignant transformation, depending on the severity of epithelial dysplasia. The characteristics of the AC are reviewed, so the clinician can provide optimal care to the patient and prevent lip cancer. The literature review was performed analyzing articles from PubMed, ScienceDirect, Google Scholar and Cochrane databases.

Keywords: Actinic Cheilitis. Oral Potentially Malignant Disorder. Lip. Ultraviolet Radiation.

Cláusula de licencia y autorización para publicación en el Repositorio Institucional

Yo, María Paz Pinos Gavilanes, en calidad de autora y titular de los derechos morales y patrimoniales del artículo académico "Actinic cheilitis: clinical, pathological and therapeutic considerations", de conformidad con el Art. 114 del CÓDIGO ORGÁNICO DE LA ECONOMÍA SOCIAL DE LOS CONOCIMIENTOS, CREATIVIDAD E INNOVACIÓN reconozco a favor de la Universidad de Cuenca una licencia gratuita, intransferible y no exclusiva para el uso no comercial de la obra, con fines estrictamente académicos.

Asimismo, autorizo a la Universidad de Cuenca para que realice la publicación de este artículo académico en el repositorio institucional, de conformidad a lo dispuesto en el Art. 144 de la Ley Orgánica de Educación Superior.

Cuenca, 01 de junio del 2021.

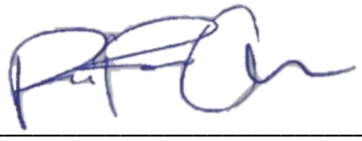
María Paz Pinos Gavilanes

C.I: 0106568868

Cláusula de Propiedad Intelectual

María Paz Pinos Gavilanes, autora del artículo académico “Actinic cheilitis: clinical, pathological and therapeutic considerations”, certifico que todas las ideas, opiniones y contenidos expuestos en el presente artículo académico son de exclusiva responsabilidad de su autor/a.

Cuenca, 01 de junio del 2021



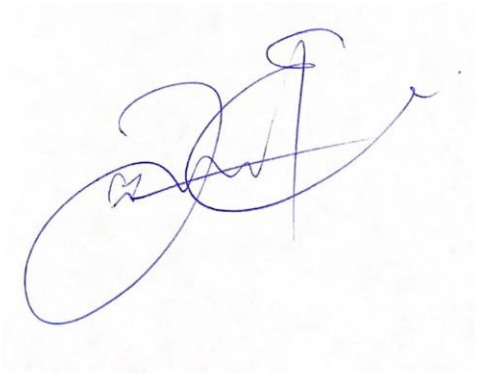
María Paz Pinos Gavilanes
C.I: 0106568868

Cláusula de licencia y autorización para publicación en el Repositorio Institucional

Yo, Daniel Esteban Pinos Gavilanes, en calidad de autora y titular de los derechos morales y patrimoniales del artículo académico "Actinic cheilitis: clinical, pathological and therapeutic considerations", de conformidad con el Art. 114 del CÓDIGO ORGÁNICO DE LA ECONOMÍA SOCIAL DE LOS CONOCIMIENTOS, CREATIVIDAD E INNOVACIÓN reconozco a favor de la Universidad de Cuenca una licencia gratuita, intransferible y no exclusiva para el uso no comercial de la obra, con fines estrictamente académicos.

Asimismo, autorizo a la Universidad de Cuenca para que realice la publicación de este artículo académico en el repositorio institucional, de conformidad a lo dispuesto en el Art. 144 de la Ley Orgánica de Educación Superior.

Cuenca, 01 de junio del 2021



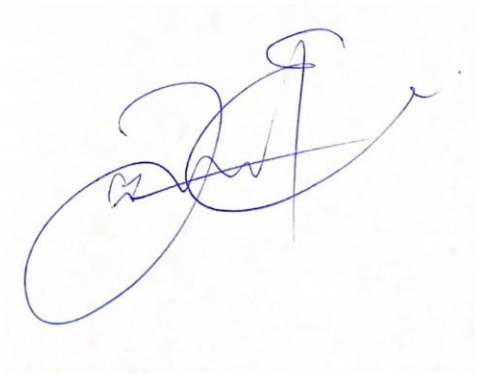
Daniel Esteban Pinos Gavilanes

C.I: 0105536031

Cláusula de Propiedad Intelectual

Daniel Esteban Pinos Gavilanes, autora del artículo académico “Actinic cheilitis: clinical, pathological and therapeutic considerations”, certifico que todas las ideas, opiniones y contenidos expuestos en el presente artículo académico son de exclusiva responsabilidad de su autor/a.

Cuenca, 01 de junio del 2021



Daniel Esteban Pinos Gavilanes

C.I: 0105536031

INTRODUCTION

Actinic cheilitis (AC) is a chronic inflammatory condition of the lip, caused by an excessive exposure to ultraviolet radiation [1-3]. Ayres first described this lesion in 1923 and it is also known as: actinic cheilosis, solar cheilosis, actinic keratosis of the lips and sailor's lip [4-8]. According to the studied population, its prevalence varies between 0.45% and 43.2%; and it is considered as a potentially malignant disorder, which can progress into squamous cell carcinoma of the lip (LSCC) [1,9-11]. It is estimated that 95% of lip cancers originate from AC; therefore, it is extremely important that general dentists recognize this entity early [2,7,12]. This manuscript presents the clinicopathological characteristics of AC and reviews the information of its etiology, treatment and predictive factors of its evolution.

ETIOLOGY

Actinic cheilitis is caused by an excessive exposure to ultraviolet (UV) radiation, both solar and artificial [1]. The lip is more susceptible to the action of UV rays than the skin, due to the epithelium of the lip is more delicate, and contains less keratin, melanin, sebaceous and sweat secretions [9]. Anatomically, the lower lip is more vulnerable to receiving high levels of radiation and consequently greater damage compared to its upper counterpart [3,13,14].

Regarding the mechanism of action of UV rays, they are considered powerful carcinogens and disturb the immune function inducing immunosuppression; UV rays are classified according to their wavelength in: UVA1 (340-400 nm), UVA2 (320-340

nm), UV-B (280-320 nm) and UV-C (200-280 nm) [1,15]. UV-A and UV-B have been related to the development of skin cancer, actinic cheilitis, and skin damage [1].

Specifically, UV-B radiation is necessary for the synthesis of vitamin D, but its excessive exposure produces direct damage to the DNA of epithelial cells, causing the DNA to act as a photophore and absorbs the energy of the incident UV radiation, resulting in the formation of cyclobutane pyrimidine dimers [1,15]. Thus, several studies performed on lip tissue have verified that UV-B radiation produces modifications in genes of important molecules, such as: p53, p21, p75NTR, Nanog, Nestin, HLA-G, VEGFR1 and VEGFR2; altering various biological processes including cell proliferation, migration, invasion and angiogenesis [1,16-23]. In addition, to direct action on cellular DNA, UV-B rays also produce oxidative stress and inflammation [1].

Moreover, UV-A causes skin aging and indirect cellular damage through the oxidative pathway mediated by photosensitizers that result in the formation of reactive oxygen species, which turn into a DNA alteration, increasing the carcinogenic action of UV-B rays [1,24].

Finally, in relation to UV-C rays of solar origin, it has been observed that they are harmless for human health because they are filtered by the Earth's atmosphere and stratosphere [24]. However, excessive exposure to artificial UV-C radiation used for the sterilization of surfaces and air of spaces, shows temporary side effects such as irritation of the cornea, conjunctiva and skin, effects that disappear after 24 to 48

hours [1,25,26]. The possible effects of artificial UVC on lip keratinocytes need to be further studied.

CLINICAL FEATURES

AC develops slowly, it is commonly confused as a characteristic of aging; initially, regions of dryness and cracking of the lip are observed, accompanied by attenuation of the demarcation between the lip mucosa and the lip skin but, without associated pain (Figure 1) [1,3,27]. As the lesion develops, the lip may become harder and experience ulceration, edema, erythema, pain, bleeding and even an accelerated growth of the entity can be verified [10,13,28].

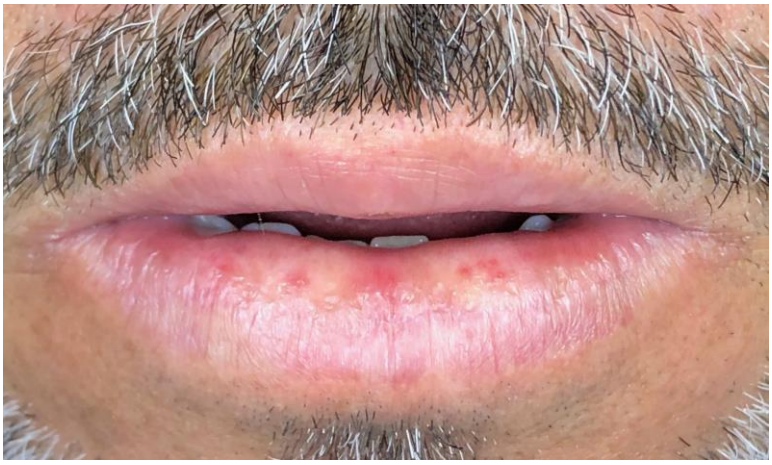


Figure 1: Actinic cheilitis. Lower lip showing dryness, cracking areas and attenuation of the demarcation between the mucosa and the skin.

AC affects the lower lip in 95% of cases, due to its higher exposure to solar radiation [1,9,11,23]. Regarding the sex of the patient, it is important to indicate that the lesion is more frequent in men than in women, possibly because men execute jobs that involve more activity outdoors and an excessive degree of sun exposure;

furthermore, it is likely that women use lipstick as a protective agent [8,9,13,24,29-36].

The majority of patients with AC are light-skinned phototype, between type I and II according to the Fitzpatrick classification [37] (Table 1). These skin tones are pale and lack of melanin, making them more susceptible to damage from UV rays; although, cases of this lesion have been identified in dark-skinned people, but their risk is lower [22,24,30,32-34,37-39].

Other factors associated with the development of this lesion are: age over 50 years, working outdoors, smoking, a history of skin cancer such as melanoma or non-melanoma, previous LSCC, alcohol consumption, immunosuppression and genetic predisposition [1,9,12,13,36,40].

TABLE 1: Fitzpatrick classification of skin phototypes based on sunburn and tanning trend.

Fitzpatrick Skin Phototype	**Skin reaction**
I - Fair-skinned	Always burn, never tan
II - Fair-skinned	Usually burn, tan less than average (with difficulty)
III - Fair-skinned	Sometimes mild burn, tan about average
IV - Light brown skin	Rarely burn, tan more than average (with ease)
V - Brown skin	Rarely burns, tans deeply
VI - Dark brown/black skin	Never burns, tans deeply

HISTOPATHOLOGY

The epithelium is characterized by the presence of hyperortokeratosis or hyperparakeratosis, it can be atrophic or acanthotic, and can also show different degrees of dysplasia [27]. The connective tissue shows an amorphous or granular basophilic material called solar elastosis, which represents alterations of the collagen and elastic fibers due to the action of UV light, in addition, a variable amount of chronic inflammatory infiltrate and dilated blood vessels are identified (Figure 2) [24,27,30,41]. Oral epithelial dysplasia is a spectrum of architectural and cytological epithelial changes caused by genetic alterations and is classified as mild, moderate, and severe or carcinoma *in situ* according to the number of epithelial thirds affected and the severity of the architectural alterations and/or cytological atypia [42]. Mild dysplasia is defined by atypia limited to the basal third, moderate dysplasia by extension to the middle third and severe dysplasia or carcinoma *in situ* by the presence of alterations up to the upper third; however, a marked atypia in the basal third of the epithelium is sufficient to grade as moderate or severe dysplasia at the time of diagnosis [42]. This classification has little intra- and interobserver reproducibility, which is why the World Health Organization recommends a consensus among pathologists to achieve reproducibility at the time of diagnosis with respect to dysplasia in the oral mucosa [42].

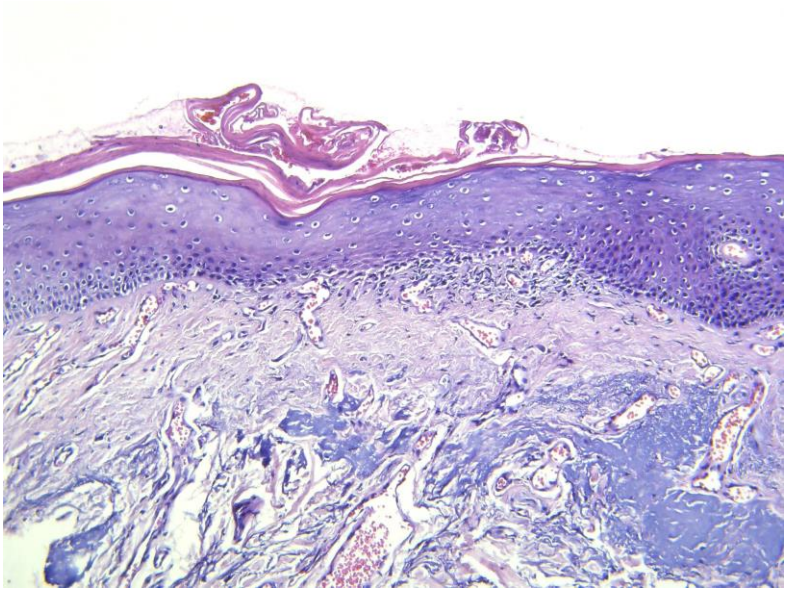


Figure 2: Microscopic details of the lip. Atrophic epithelium with hyperortokeratosis and hyperchromatic cells on the basal layer. Note the presence of areas of solar elastosis on the connective tissue. (Hematoxylin and eosin. Original magnification X200).

PROGNOSIS

Between 3-30% of AC cases can transform into invasive SCC, in periods of 1 to 30 years according to different studies [2,3,12,31,33]. Thus, the prognosis of AC is variable and depends mainly on the degree of epithelial dysplasia and on changes in the patient's habits such as reduction in sun exposure, use of sunscreen, hats and caps [9,10].

Regarding microscopically verifiable prognostic factors, it is important to note that the histological changes of AC are not evenly distributed in the vermilion of the lip, even in cases where the clinical presentation of AC is homogeneous [3]. The presence of the epithelial dysplasia is the principal predictive factor of malignant transformation of this oral potentially malignant lesion, transformation rates of 24.98% have been verified in cases with severe dysplasia, 12.57% in cases with

moderate dysplasia, and 5.23% in lesions with mild dysplasia [42,43]. Together, these reasons reinforce the necessity to perform the histopathological analysis of any suspicious lesion [9].

Otherwise, although the presence of dysplasia is correlated to the development of SCC, many lesions do not progress to malignancy, being low the reproducibility of the diagnosis of dysplasia the cause of this lack of accuracy as a prognostic factor [42,44,45]. In this context, different molecules have been analyzed as possible biomarkers for the prognosis of AC, including:

The p53 protein that regulates the G1/S checkpoint of the cell cycle, mutations in TP53 gene make p53 unable to control cell proliferation, resulting in inefficient DNA repair and allowing many cells exposed to mutagens to replicate the genetic material damaged, spreading the changes incorporated into the genome [1,3]. 90% of SCC cases have specific UV mutations of the TP53 gene, consequently its overexpression significantly increases the risk of AC transforming to a SCC; also, the expression of p53 leads to an increase in the expression of p21, suggesting that it may also be involved in carcinogenesis processes [16].

Cancer stem cells (CSCs) that represent a small and rare subpopulation of cells capable of self-renewal, they have an unlimited replication potential and a unique ability to initiate and maintain tumor growth, for this reason are also known as cell tumor initiators [18]. Some surface markers help us to identify CSCs, such as the p75 neurotrophin receptor (p75NTR) which is overexpressed as the degree of epithelial dysplasia increases in cases of AC and LSCC [18].

Nanog protein is a transcription factor present in embryonic stem cells, which can modulate the proliferation, invasiveness and metastasis of neoplastic cells [46]. Nestin protein is considered a biomarker to identify CSCs in epithelial neoplasms and has key roles in the differentiation, proliferation, migration, invasion, metastasis and survival of malignant neoplastic cells, by regulating the cytoskeleton and progenitor cells [47]. Both Nanog and Nestin have shown a positive relationship with CSCs, in cases of AC there is overexpression of these proteins [19].

HLA-G protein or human leukocyte antigen G is an immune control protein that is dysregulated in the presence of tumors and precursor disorders; cases of AC have exhibited higher expressions levels of this protein when compared to normal epithelium of the lip [21]. In addition, Langerhans CD1a + cells are significantly reduced in cases of AC compared to normal oral epithelium [20].

The increase in vascularization is significant during the transition from normal oral mucosa to different degrees of epithelial dysplasia, receptors for vascular endothelial growth factor such as VEGFR1 and VEGFR2 are overexpressed in AC epithelium [22,23].

TREATMENT

The main objective of the treatment of AC is the removal of the altered epithelium, which can be achieved by non-surgical and surgical techniques.

Non-surgical Treatments

5- Fluorouracil (5-FU)

5-FU is an antimetabolite drug used as a systemic chemotherapeutic agent; it blocks DNA synthesis by inhibiting the enzyme thymidylate synthase [27]. This agent affects neoplastic cells due to their increased metabolic activity [6]. For the management of AC it has been used topically, several presentations are available (solution, cream and microsponge cream) and different concentrations of 0.5% to 5%; the use of one to two times a day is suggested for a period of several weeks [6]. Immediate side effects include erythema, edema, ulceration and pain of the lips, in few cases difficulty eating and speaking; these symptoms often persist throughout the course of therapy and can cause a decrease in patient adherence to prescribed treatment [6,48]. With the aim of reducing the side effects of 5-FU, its application was proposed only once a week; however, efficacy in eliminating the lesion was not verified clinically or pathologically [49]. Furthermore, Robinson (1989) found that, although this drug can clinically eliminate AC lesions, recurrent areas with the presence of epithelial dysplasia can be seen histologically in 60% of cases [48]. The recurrence rate presented with 5-FU reinforces the need for long-term monitoring of patients treated with this drug.

Imiquimod

Imiquimod works as an immune modulator that binds to the Toll-like receptor 7 (TLR-7), its activation provokes intracellular signaling, which leads to the release of interferon and pro-inflammatory cytokines; inducing apoptosis of abnormal cells [27]. Topical application of 5% imiquimod has side effects similar to 5-FU that include: erythema, edema, suppuration, crusting, erosion, superficial ulceration and pain that can be mild to severe [6,27]. Due to the side effects, patient compliance can become

a major factor impairing successful imiquimod treatment [6]. The application of imiquimod three times per week over the course of four to six weeks, demonstrated to be clinical effectively but the histological recurrence has not been proven yet [6,50,51].

Diclofenac

Diclofenac is a non-steroidal anti-inflammatory agent that acts by decreasing the dynamics of the proliferative cell cycle by inhibiting the formation of prostaglandins [6,27]. Topical application has been proposed as a less aggressive treatment alternative, 3% diclofenac gel for a period of 6 weeks has proven to be efficient [52]. Side effects can include edema, erythema and a burning sensation [52]. However, new studies are necessary to know the recurrence after the application of this agent.

Photodynamic Therapy

Photodynamic therapy (PDT) consists of application of an photosensitizing agent that is activated by a visible light source and produces oxygen free radicals, these destabilize the cell membrane and organelles, inducing apoptosis [53]. During treatment, first, crusts and scales are carefully removed from the lip; a photosensitizer such as 5-aminolevulinic acid (5-ALA) is applied locally, this takes approximately two hours to be absorbed by potentially malignant cells, its intracellular presence allows the selective absorption of light and subsequently the destruction of the injured tissue [6,54]. PDT may have some limitations because it can be complex, time consuming, expensive, and it produces side effects such as erythema, edema, burning sensation and pain in the lip as it is a very sensitive area

[54]. Daylight PDT is an effective alternative conventional therapy, pain is minimal or nonexistent and has a lower cost of treatment [54,55]. However, the persistence of dysplasia after PDT therapy has been demonstrated, with a high rate of recurrence up to 62% [56].

Surgical Treatments

Vermilionectomy

Vermilionectomy is considered an excisional biopsy because consists of the complete removal of all the epithelium that covers the lip, using a scalpel [3,6]. There are variations of this procedure, for example: a simple vermilionectomy involves removal of the vermilion only at the level of the orbicular muscles of the mouth, while a modified vermilionectomy may include removal of adjacent glands and muscle tissue [6]. It is considered an invasive treatment and several side effects have been described, including delayed re-epithelialization, initially non-esthetic appearance of the lip, pain in the healing phase, edema, secondary infection, scars, paresthesia and dysesthesia and necrosis [27,29,48]. Despite the adverse effects, this is the treatment of choice, demonstrating excellent results with complete clinical and pathological resolution of the lesion and because is the only therapy that generates a surgical specimen in which can be performed the microscopically verification of the dysplasia or the early detection of a possible invasive tumor [2,3,6,48,51].

Carbon Dioxide Laser Ablation

The carbon dioxide (CO_2) laser creates an infrared light with a wavelength of 10.600 nm that produces a thermal effect on the injured tissue, heating intracellular and

extracellular water to 100°C, which causes vaporization and alteration of the cell membrane and subsequently leads to cell death [6]. The treated epithelium is removed with a moistened cotton swab or gauze [6]. A distinctive advantage of CO2 laser therapy is that it is a procedure that allows direct visualization of the lip during treatment because it is a bloodless procedure, leaves the underlying muscle intact, also has fewer adverse effects than vermilionectomy [6,57,58]. Furthermore, the efficacy of the CO2 laser has high effectiveness rates with values similar to those obtained through vermilionectomy, and investigations with post-therapeutic biopsies have shown few recurrences of AC treated with CO2 laser [6,48,59,60].

Cryosurgery

Focal lesions of AC has been successfully treated by cryosurgery since the smooth surface and moisture of the mucous membranes allow fast freezing, it is done by applying liquid nitrogen to the lesion, this acts at the cellular level, causing crystallization and subsequent cell disruption by metabolic flux; it also functions at the vascular level by causing thrombosis, ischemia, and cell necrosis [61]. The advantages of cryosurgery are several, it is an inexpensive treatment and does not require much operator skill, it can be performed without local anesthesia and it is fast; however, a disadvantage is that there is no standardization for the application of cryogen (using a spray, flat attachment, or cotton tip applicator) and application time [6]. Possible adverse effects of cryosurgery include postoperative edema, pain during and after treatment, local irritation, redness, headache induction, long-term scarring, hyperpigmentation, hypopigmentation, and local neuropathy [6,27].

Another disadvantage of cryosurgery is that it does not eliminate all the lesions treated; Lubritz et al. (1989) in their study found a recurrence of 3.8% [6,62].

Electrosurgery

Electrosurgery is also a relatively inexpensive, simple, and useful therapeutic option for the treatment of focally localized AC [6]. In this method, an electrode is used to apply an electrical current to the labial surface previously locally anesthetized, then the charred epithelium is removed by means of a gauze moistened with saline solution [6,58]. The disadvantages of this technique includes a prolonged healing time that on average is 8 days longer when compared to areas treated by CO2 laser; in addition, the patient may manifest a burning sensation and the possible formation of scars in the adjacent tissue [57,58]. Regarding recurrence rates, a study by Laws et al. (2000) revealed that only two of six patients showed histological improvement after treatment with electrosurgery; further long-term studies are needed on the clinical and histological efficacy of this modality[6,58].

In summary, the selection of therapy for AC should be carried out individually for each case, considering the possible adverse effects, the aesthetic wishes of the patient and above all; scientific evidence and microscopically findings obtained from the analysis of incisional biopsies [6,51]. Therapies that are more aggressive should be considered in extensive AC, with poorly defined borders and/or with severe dysplasia, while, conservative methods can be selected for those focal cases, without dysplasia [51]. Furthermore, regardless of the treatment carried out, long-

term postoperative follow-up of patients diagnosed with AC should be performed, with visits every 6 months for the first 2 years and subsequent annual controls [2,6].

CONCLUSION

In conclusion, considering that actinic cheilitis is a potentially malignant disorder; the dentist must attempt its early detection, paying particular attention to the clinical examination of the lip, since suspicious lesions must be analyzed microscopically to establish the definitive diagnosis. The main therapeutic options are CO2 laser ablation and vermilionectomy, due to their high effectiveness and, in the case of vermilionectomy, the possibility of the histopathological study of the epithelium. Finally, patient orientation regarding preventive measures for sun protection and their long-term post-therapeutic monitoring is mandatory.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Dancyger A, Heard V, Huang B, et al. Malignant transformation of actinic cheilitis: A systematic review of observational studies. Journal of investigative and clinical dentistry. 2018;9(4):e12343.

2. Carvalho MdV, de Moraes SLD, Lemos CAA, et al. Surgical versus non-surgical treatment of actinic cheilitis: A systematic review and meta-analysis. Oral diseases. 2019;25(4):972-981.

3. Vieira RAMAR, Minicucci EM, Marques MEA, et al. Actinic cheilitis and squamous cell carcinoma of the lip: clinical, histopathological and immunogenetic aspects. Anais brasileiros de dermatologia. 2012;87(1):105-114.

4. AYRES S. Chronic actinic cheilitis. Journal of the American Medical Association. 1923;81(14):1183-1186.

5. Lugović-Mihić L, Pilipović K, Crnarić I, et al. Differential Diagnosis of Cheilitis–How to Classify Cheilitis? Acta Clinica Croatica. 2018;57(2):342-351.

6. Shah AY, Doherty SD, Rosen T. Actinic cheilitis: a treatment review. Int J Dermatol. 2010 Nov;49(11):1225-34.

7. Osorio CH, Palma BF, Cartes-Velásquez R. Queilitis actínica: aspectos histológicos, clínicos y epidemiológicos. Revista cubana de estomatología. 2016;53(2):45-55.

8. Gonzaga AKG, Mafra RP, da Silva LP, et al. Actinic cheilitis: Morphometric parameters and its relationship with the degree of epithelial dysplasia. Acta Histochem. 2020 Jan;122(1):151452.

9. de Santana Sarmento DJ, da Costa Miguel MC, Queiroz LM, et al. Actinic cheilitis: clinicopathologic profile and association with degree of dysplasia. Int J Dermatol. 2014 Apr;53(4):466-72.

10. Santos RFD, Oliveira RL, Gallottini M, et al. Prevalence of and Factors Associated with Actinic Cheilitis in Extractive Mining Workers. Braz Dent J. 2018 Mar-Apr;29(2):214-221.

11. Maia HC, Pinto NA, Pereira Jdos S, et al. Potentially malignant oral lesions: clinicopathological correlations. Einstein (Sao Paulo). 2016 Jan-Mar;14(1):35-40.

12. Lai M, Pampena R, Cornacchia L, et al. Treatments of actinic cheilitis: A systematic review of the literature. J Am Acad Dermatol. 2020 Sep;83(3):876-887.

13. Markopoulos A, Albanidou-Farmaki E, Kayavis I. Actinic cheilitis: clinical and pathologic characteristics in 65 cases. Oral Dis. 2004 Jul;10(4):212-6.

14. Rodriguez-Blanco I, Florez A, Paredes-Suarez C, et al. Use of lip photoprotection in patients suffering from actinic cheilitis. Eur J Dermatol. 2019 Aug 1;29(4):383-386.

15. Suozzi K, Turban J, Girardi M. Cutaneous Photoprotection: A Review of the Current Status and Evolving Strategies. Yale J Biol Med. 2020 Mar;93(1):55-67.

16. de Sousa Lopes MLD, de Oliveira DHIP, de Santana Sarmento DJ, et al. Correlation between cell cycle proteins and hMSH2 in actinic cheilitis and lip cancer. Archives of dermatological research. 2016;308(3):165-171.

17. Correa GT, Bernardes VF, de Sousa SF, et al. Lip cancer and pre-cancerous lesions harbor TP53 mutations, exhibit allelic loss at 9p, 9q, and 17p, but no BRAFV600E mutations. Tumour Biol. 2015 Nov;36(11):9059-66.

18. Custodio M, Pelissari C, Santana T, et al. Expression of cancer stem cell markers CD44, ALDH1 and p75NTR in actinic cheilitis and lip cancer. Eur Arch Otorhinolaryngol. 2018 Jul;275(7):1877-1883.

19. Scotti FM, Mitt VC, Vieira DS, et al. Expression of stem cell markers Nanog and Nestin in lip squamous cell carcinoma and actinic cheilitis. Oral Dis. 2018 Oct;24(7):1209-1216.

20. Gomes JO, de Vasconcelos Carvalho M, Fonseca FP, et al. CD1a+ and CD83+ Langerhans cells are reduced in lower lip squamous cell carcinoma. J Oral Pathol Med. 2016 Jul;45(6):433-9.

21. Lopes M, Gonzaga AKG, Mosconi C, et al. Immune response and evasion mechanisms in lip carcinogenesis: An immunohistochemical study. Arch Oral Biol. 2019 Feb;98:99-107.

22. Barbosa NG, Souza LB, Nonaka CF, et al. Evaluation of hypoxia, angiogenesis, and lymphangiogenesis in actinic cheilitis. Int J Dermatol. 2016 Nov;55(11):e573-e578.

23. Ariotti C, Wagner VP, Salvadori G, et al. VEGFR1 and VEGFR2 in lip carcinogenesis and its association with microvessel density. Tumour Biol. 2015 Sep;36(9):7285-92.

24. Puga P. Parámetros de riesgo de la queilitis actínica crónica Universidad de Granada 2009.

25. Buonanno M, Welch D, Shuryak I, et al. Far-UVC light (222 nm) efficiently and safely inactivates airborne human coronaviruses. Sci Rep. 2020 Jun 24;10(1):10285.

26. Zaffina S, Camisa V, Lembo M, et al. Accidental exposure to UV radiation produced by germicidal lamp: case report and risk assessment. Photochem Photobiol. 2012 Jul-Aug;88(4):1001-4.

27. Salgueiro AP, de Jesus LH, de Souza IF, et al. Treatment of actinic cheilitis: a systematic review. Clin Oral Investig. 2019 May;23(5):2041-2053.

28. Kwon NH, Kim SY, Kim GM. A case of metastatic squamous cell carcinoma arising from actinic cheilitis. Ann Dermatol. 2011 Feb;23(1):101-3.

29. Castineiras I, Del Pozo J, Mazaira M, et al. Actinic cheilitis: evolution to squamous cell carcinoma after carbon dioxide laser vaporization. A study of 43 cases. J Dermatolog Treat. 2010 Jan;21(1):49-53.

30. Cavalcante AS, Anbinder AL, Carvalho YR. Actinic cheilitis: clinical and histological features. J Oral Maxillofac Surg. 2008 Mar;66(3):498-503.

31. de Oliveira Bezerra HI, Gonzaga AKG, da Silveira EJD, et al. Fludroxycortide cream as an alternative therapy for actinic cheilitis. Clin Oral Investig. 2019 Oct;23(10):3925-3931.

32. Gonzaga AKG, de Oliveira PT, da Silveira ÉJD, et al. Diclofenac sodium gel therapy as an alternative to actinic cheilitis. Clinical oral investigations. 2018;22(3):1319-1325.

33. Lopes ML, Nonaka CF, Queiroz LM, et al. Pattern of galectins expression in actinic cheilitis with different risks of malignant transformation. J Oral Pathol Med. 2016 Sep;45(8):621-6.

34. Mello FW, Melo G, Modolo F, et al. Actinic cheilitis and lip squamous cell carcinoma: Literature review and new data from Brazil. J Clin Exp Dent. 2019 Jan;11(1):e62-e69.

35. Orozco P, Vásquez S, Venegas B, et al. Prevalencia de queilitis actínica en trabajadores expuestos a radiación ultravioleta en Talca, Chile. Revista clínica de periodoncia, implantología y rehabilitación oral. 2013;6(3):127-129.

36. Ríos P, Maldonado C, Norambuena P, et al. Prevalencia de queilitis actínica en pescadores artesanales, Valdivia, Chile. International journal of odontostomatology. 2017;11(2):192-197.

37. Fitzpatrick TB. The validity and practicality of sun-reactive skin types I through VI. Archives of dermatology. 1988;124(6):869-871.

38. Rodriguez-Blanco I, Florez A, Paredes-Suarez C, et al. Actinic Cheilitis: Analysis of Clinical Subtypes, Risk Factors and Associated Signs of Actinic Damage. Acta Derm Venereol. 2019 Sep 1;99(10):931-932.

39. Muse ME, Crane JS. Actinic Cheilitis. StatPearls. Treasure Island (FL)2020.

40. Bentley JM, Barankin B, Lauzon GJ. Paying more than lip service to lip lesions. Can Fam Physician. 2003 Sep;49:1111-6.

41. Santana T, Matuck B, Tenorio JR, et al. Can immunohistochemical biomarkers distinguish epithelial dysplasia degrees in actinic cheilitis? A systematic review and meta-analysis. Med Oral Patol Oral Cir Bucal. 2020 Jan 1;25(1):e106-e116.

42. El-Naggar AK, Chan JK, Grandis JR, et al. WHO classification of head and neck tumours. International Agency for Research on Cancer (IARC); 2017.

43. Dong Y, Chen Y, Tao Y, et al. Malignant transformation of oral leukoplakia treated with carbon dioxide laser: a meta-analysis. Lasers Med Sci. 2019 Feb;34(1):209-221.

44. Nagata G, Santana T, Queiroz A, et al. Evaluation of epithelial dysplasia adjacent to lip squamous cell carcinoma indicates that the degree of dysplasia is not associated with the occurrence of invasive carcinoma in this site. J Cutan Pathol. 2018 May 8.

45. Pilati S, Bianco BC, Vieira D, et al. Histopathologic features in actinic cheilitis by the comparison of grading dysplasia systems. Oral Dis. 2017 Mar;23(2):219-224.

46. Watanabe M, Ohnishi Y, Inoue H, et al. NANOG expression correlates with differentiation, metastasis and resistance to preoperative adjuvant therapy in oral squamous cell carcinoma. Oncol Lett. 2014 Jan;7(1):35-40.

47. Neradil J, Veselska R. Nestin as a marker of cancer stem cells. Cancer Sci. 2015 Jul;106(7):803-11.

48. Robinson JK. Actinic cheilitis. A prospective study comparing four treatment methods. Arch Otolaryngol Head Neck Surg. 1989 Jul;115(7):848-52.

49. Wright K, Dufresne R. Actinic cheilitis. Dermatol Surg. 1998 Apr;24(4):490-1.

50. Smith KJ, Germain M, Yeager J, et al. Topical 5% imiquimod for the therapy of actinic cheilitis. J Am Acad Dermatol. 2002 Oct;47(4):497-501.

51. Varela-Centelles P, Seoane-Romero J, Garcia-Pola MJ, et al. Therapeutic approaches for actinic cheilitis: therapeutic efficacy and malignant transformation after treatment. Int J Oral Maxillofac Surg. 2020 Oct;49(10):1343-1350.

52. Ulrich C, Forschner T, Ulrich M, et al. Management of actinic cheilitis using diclofenac 3% gel: a report of six cases. Br J Dermatol. 2007 May;156 Suppl 3:43-6.

53. Chaves YN, Torezan LA, Lourenco SV, et al. Evaluation of the efficacy of photodynamic therapy for the treatment of actinic cheilitis. Photodermatol Photoimmunol Photomed. 2017 Jan;33(1):14-21.

54. Levi A, Hodak E, Enk CD, et al. Daylight photodynamic therapy for the treatment of actinic cheilitis. Photodermatol Photoimmunol Photomed. 2019 Jan;35(1):11-16.

55. Wiegell SR, Wulf HC, Szeimies RM, et al. Daylight photodynamic therapy for actinic keratosis: an international consensus: International Society for Photodynamic Therapy in Dermatology. J Eur Acad Dermatol Venereol. 2012 Jun;26(6):673-9.

56. Berking C, Herzinger T, Flaig MJ, et al. The efficacy of photodynamic therapy in actinic cheilitis of the lower lip: a prospective study of 15 patients. Dermatol Surg. 2007 Jul;33(7):825-30.

57. Kim SM, Myoung H, Eo MY, et al. Proper management of suspicious actinic cheilitis. Maxillofac Plast Reconstr Surg. 2019 Dec;41(1):15.

58. Laws RA, Wilde JL, Grabski WJ. Comparison of electrodessication with CO2 laser for the treatment of actinic cheilitis. Dermatol Surg. 2000 Apr;26(4):349-53.

59. Whitaker DC. Microscopically proven cure of actinic cheilitis by CO2 laser. Lasers Surg Med. 1987;7(6):520-3.

60. de Godoy Peres FF, Aigotti Haberbeck Brandao A, Rodarte Carvalho Y, et al. A study of actinic cheilitis treatment by two low-morbidity CO2 laser vaporization one-pass protocols. Lasers Med Sci. 2009 May;24(3):375-85.

61. Ishida CE, Ramos-e-Silva M. Cryosurgery in oral lesions. Int J Dermatol. 1998 Apr;37(4):283-5.

62. Lubritz RR, Smolewski SA. Cryosurgery cure rate of premalignant leukoplakia of the lower lip. J Dermatol Surg Oncol. 1983 Mar;9(3):235-7.