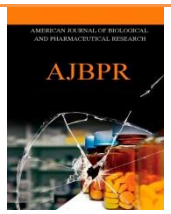
e-ISSN - 2348-2184
Print ISSN - 2348-2176

AMERICAN JOURNAL OF BIOLOGICAL AND PHARMACEUTICAL RESEARCH

Journal homepage: www.mcmed.us/journal/ajbpr



A COMPREHENSIVE REVIEW ON ACTINIC CHELITIS

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Article Info

Received 29/04/2015
Revised 16/05/2015
Accepted 19/05/2015

Key words: -Actinic cheilitis, Diclofenac, laser therapy, Chloroquine, Photodymamic therapy, Vermillion border.

ABSTRACT

Actinic cheilitis is a potentially premalignant condition caused through exposure to sunlight, which involves the vermillion border of the lip and is readily diagnosed clinically. . Modern times has seen an increase in number of people working in fields in the rural areas of the country, leading to an increase in sunlight-induced skin diseases in this group of the population. Early identification of the lesion can allow for the development of novel treatment strategies for patients to prevent the disease progression and its malignant transformation. The present article reviews different treatment modalities in management of actinic chelitis.

INTRODUCTION

Actinic cheilitis also called as actinic cheilosis or solar cheilitis, is a potentially malignant condition of the lip vermillion caused by long-time exposure to ultraviolet light. This lesion affects mostly the lower lip and is more frequent in individuals with fair skin, males and those who are regularly in the sun. In the south region of Brazil, due to the tropical climate and the European descent of large part of the population, this lesion assumes great importance. The relationship between lip cancer and sun exposure was described by Ayres in 1923 [1]. It occur more frequently in pale people, particularly in those with fair complexions, persons with albinism, males, the elderly, those who live at high altitudes or close to the equator, and of course, those who by reason of their occupations or their leisure activities have excessive exposure to the sun. The vermilion border of the lower lip may also be more vulnerable to sunlight-induced lesions because its epithelium is thin, has a thin keratin layer and has lower melanin content. Actinic cheilitis is similar to actinic keratosis of the skin due to similar etiology of the two diseases. The disease is caused due to long-time exposure to the lower lip vermilion to ultraviolet light and the chances of development of oral squamous cell carcinoma. The lower lip vermilion is most affected as it lies at right angles to the sun during mid day and the epithelium is also thin with less melanin content. Upper lip involvement may be rarely seen in patients with bimaxillary protrusion. Tobacco chewers and use of other chemical carcinogens is thought to have a synergistic effect in the development of this condition. Additional factors include poor oral hygiene & chronic lip irritation. The condition is usually asymptomatic but the patient may sometimes complaint of tightness in lip. Clinically, it is observed as mottling of the lip with atrophic areas or shallow erosions and rough, scaly, flaky keratotic patches on some parts, or on the entire exposed portion of the lip. Sometimes small wrinkles can be seen in the vermilion border of the lip.

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Fine sandpaper like feeling can be appreciated on palpation [2]. There are two clinical forms of actinic chelitis: acute and chronic. The acute form is more common in young individuals and occurs after excessive exposure to the ultraviolet light, while the chronic form is a cumulative and irreversible alteration. In chronic actinic chelitis, the lip appears parched and atrophic, with dyschromic areas, white or gray plaques (Fig 1) and recurrent erosions. The lesion is usually asymptomatic, but can in some cases be accompanied by a burning sensation, numbness and pain. Actinic cheilitis is also known as actinic keratosis of the lip. Its similarity with actinic keratosis of the skin lies in the etiology of both diseases, exposure to solar radiation and the possibility of development of squamous cell carcinoma. It is manifested through desiccation, erosion and loss of the lower lip border. The estimated time for the development of lip cancer is 20 to 30 years, but this time is shorter for some patients. Patients at risk of developing lip cancer are usually fair-skinned smokers who are older than 50 and have a history of sun exposure.

Squamous cell carcinoma of the lip almost always develops in pre-existing lesions of actinic cheilitis. It affects the lower lip in more than 90% of the cases. Some signs of malignancy are hardened area, ulcer, persistent erythema and hyperkeratotic areas [3]. Any of these changes indicate the need for biopsy. Squamous cell carcinoma is the most common malignant neoplasia of the lip and represents about 15% to 40% of the cases of oral cancer. Actinic cheilitis must be treated because of the risk of developing squamous cell carcinoma and the consequent potential for causing metastasis. While squamous cell carcinoma of the lip causes metastasis in approximately 11% of the cases, the chances that this same tumor of the skin when derived from actinic keratosis develops into metastasis are less than 1%.

Smoking and infection of the lip by the human papillomavirus may cause additional cytogenetic alterations and further increase the risk of actinic cheilitis becoming carcinomatous [4]. The most important risk factor for actinic cheilitis is outdoor activity and skin type. Also socioeconomic status, lifestyle, smoking, dietary habits, and genetic predisposition are associated with lip cancer.It primarily affects people with Fitzpatrick skin types I and II as a result of chronic exposure to solar irradiation. It has also been reported that chronic recurrent actinic cheilitis associated with hereditary polymorphic light eruption appears to be a specific characteristic of photosensitivity occurring in American Indians. Although many studies reported that actinic chelitis is prevalent in fair-skinned people, a recent study has demonstrated that it is not exclusive to fair skinned individuals [5].

Apart from these risk factors, dental and skeletal characteristics like a prognathic maxilla also contribute to more exposure of lips to sunlight. Ultraviolet-B radiation of sunlight, with the wavelength ranging from 290-320 nm, causes superficial burning of the skin and is responsible for sun-induced changes of the lip. The lip has less protection than the skin because the epithelium is thinner, lacks thicker keratin, has less melanin, and fewer secretions from the sebaceous and sweat glands. Actinic cheilitis presents clinically as a localized or diffuse lesion of the lips that may be white red or red and white. White areas represent areas of hyperkeratinization, whereas, red areas represent areas of atrophy. Lips appear dry with erythema, sometimes with swelling and cracking [6].

Etiopathogenesis

The wavelength of ultraviolet (UV) light lies within the range of 100–400 nm of the electromagnetic spectrum. UV light is classified as UV-A, -B and -C. UVC is in the range of 100–290 nm; UVB, 290–320 nm; and UVA, about 320–400 nm. Sunlight UVC is almost completely filtered out by the atmosphere. Both UVA and UVB can contribute to ageing of the skin by damaging collagen, breaking down vitamin A, by causing local immunosuppression and by ionisation, which releases hydroxyl and oxygen radicals and thus contributes indirectly to DNA damage. UVB from the sun, which is only partly filtered out by the atmosphere, can cause mutagenic changes; a common event of this kind is the formation of aberrant covalent bonds between adjacent cytosine bases in epithelial DNA [7].

Cells with these dimers of cytosine in their DNA then propagate, giving rise to clones of mutated cells. Actinic keratosis of the skin is thus a primarily UVB-induced intra-epithelial neoplasm: the analogous lesion of the vermilion border of the lip is called actinic cheilitis. In the initiation stage of actinic-induced carcinogenesis following significant exposure to the sun, UVB causes mutations in the epithelial p53 tumour-suppressor gene that result in the dysregulation of its functions. If there is only limited exposure to UVB, p53 can retain sufficient functionality to arrest the cell cycle, permitting activation of repair processes of cellular DNA before the cell enters the phase of DNA synthesis.

A cell with repaired DNA can then proceed through the rest of the cell cycle to cell division. Very severe UVB exposure, in contrast, can damage the DNA sufficiently to render it beyond repair, and p53 then activates cellular pathways leading apoptosis. UVB-induced dysregulation of the function of the tumour-suppressor gene p53 results in genomic instability, making the cells susceptible to further critical UVB-induced genetic alterations with ultimate malignant transformation of the affected cells.

It is evident that UVB is a complete carcinogen since it not only initiates the genetic alteration of epithelial cells but also subsequently promotes the expansion of clones of transformed cells, which then display all the characteristics of malignancy [8].

Histopathologic features

Actinic cheilitis may show epithelial changes of simple keratosis, different grades of epithelial dysplasia, in-situ carcinoma or even invasive squamous cell carcinoma, all of which at some stage may have similar clinical appearances. It cannot be predicted whether or when actinic cheilitis will progress to squamous cell carcinoma. Consequently, a clinical diagnosis of actinic cheilitis must always be supported by histopathological evidence, but a single biopsy result may not be conclusive, and the prudent clinician would be well advised to take a biopsy from more than one site [9].

Discussion

The main objectives of treatment of chronic actinic chelitis are to prevent the development of squamous cell carcinoma, improve the aesthetic picture and diminish the inconvenience caused by lip erosions, crusts and roughness. There are various therapeutic modalities with the aim of removing the altered epithelium of these lesions such as trichloroacetic acid, imiquimod and retinoids. Other treatments include surgical excision with cold scalpel (vermilionectomy), vaporization with CO2 or Er: YAG laser, cryosurgery, dermabrasion, electro dissection and photodynamic therapy (PDT) with aminolevulinic acid. These treatments are very destructive and frequently cause considerable discomfort to the patients, which have stimulated the development of effective and economically viable alternatives for the treatment of actinic chelitis [10].

Vermilionectomy is an excellent alternative for treatment of actinic cheilitis, since it is easy to perform it and since it provides satisfactory aesthetic results according to several authors. According to Spira and Hardy in 1964, vermilionectomy was initially described by Bernard and Huette in 1869 [11]. Kwapis and Gibson described vermilionectomy in 1956 as excision of all or part of the vermilion of the lip, with mucosal advancement and its suture to the skin for closure of the defect [12]. It is performed under local anesthesia, the whole vermilion of the lower lip is resected, without touching the orbicularis muscle. The mucosa is advanced toward the skin to be sutured and thus close the defect. Some postoperative complications are hematoma, suture dehiscence and hypoesthesia. In vermilionectomy using the conventional technique, the scar that results from resection of the vermilion border is linear, which can lead to scar retraction and consequent unaesthetic scar. In order to avoid scar retraction, Fernandez vozmediano in 1989, proposed the use of vermilionectomy forming a broken line, a technique called W-plasty, having published three cases involving this technique. Surgical vermilionectomy provides an alternative method for treatment of actinic chelitis, especially in the presence of severely dysplastic features, although as with other invasive surgery techniques, it is associated with intraoperative difficulty, bleeding, and pain and postoperative edema, scarring, and dysesthesia. Combining the low complexity of nonsurgical techniques with the efficacy of surgical procedures, laser therapy provides a promising treatment option for actinic chelitis [13]. CO_2 laser ablative treatments for actinic chelitis have been studied extensively and have demonstrated remarkable curative and cosmetic results. It is also associated with low recurrence; three of 43 patients were found to have recurrences, of which two developed squamous cell carcinoma [14].

Nonetheless, secondary complications, including pain, edema, delayed re-epithelialisation, and scarring, have been reported, probably owing to its deep ablative thermal effects. The 2,940-nm Er: YAG was introduced as an alternative solution. The properties of the Er: YAG laser prevent it from being absorbed as deeply as the 10,600-nm CO2 laser, which results in less postoperative morbidity, but because of its high water absorption, the Er: YAG laser has insufficient coagulative effects, resulting in higher rates of intraoperative bleeding [15].

Fractional photo thermolysis offers a novel approach for the treatment of actinic chelitis, because it overcomes the detrimental effects of ablative laser surgery and the poorer efficacy of conservative nonsurgical techniques. As with the 1,550-nm erbium-doped fiber laser, the mechanism behind the 1927-nm thulium laser involves the emission of a concentrated beam that produces multiple zones of microscopic thermal injury known as microscopic treatment zones (MTZs). Within the first few hours of the formation of these MTZs, the viable epidermis surrounding each MTZ begins to regenerate and aids in the healing process. The preservation of the epidermal barrier may account for the minimal side effects and the faster healing process than with ablative laser resurfacing. These unique properties have rendered the 1,550-nm fractional laser a well-established modality for the treatment of such common conditions as acne scars, surgical scars, melasma, and photodamaged skin. The recent introduction of the 1,927-nm thulium fractional laser provides the technology of a superficial wavelength that penetrates only the epidermis and upper dermis, providing a nonablative resurfacing that is ideal for the treatment of discoloration and uneven texture. Ongoing studies show the superior efficacy of the 1,927-nm thalium fractional laser for the treatment of photodamaged skin, including actinic keratosis [16,17].

The use of the 1,927-nm thulium fractional laser results in excellent clearance of actinic keratosis, with a mean clearance rate of 62.7% after the first treatment, 84.3% after the second treatment, and 88.5% after three treatments. A recent multicenter study reviewing 15 patients with actinic chelitis who had been treated using the 1,927-nm thulium fractional laser showed 76% to 100% (9 patients) and 51% to 75% (6 patients) improvement after

one or two treatments. The only side effects seen in this study were transient erythema and edema lasting 1 to 4 and 1 to 3 days, respectively [18].

Cryosurgery and electrosurgery are readily accessible procedures with proven efficacy, but their use is generally limited to focal areas of cheilitis in order to prevent edema and ulcerations [19].

PDT is another effective treatment option, especially for patients who cannot tolerate invasive techniques. Nonetheless, the widespread use of PDT for actinic chelitis is precluded because of pain and a burning sensation during light exposure and an extended recovery period, with inflammation lasting up to 15 days. It has recently been reported that photodynamic therapy using the methyl-ester of aminolevulinic acid as a photosensitising agent is a very effective treatment modality for actinic cheilitis. It is well tolerated by patients and provides excellent cosmetic outcomes [20].

Conservative, nonsurgical treatments that have been reported include topical applications of trichloroacetic acid, 5-fluorouracil, imiquimod, and diclofenac. Although these treatments are feasible, they are limited by the development of erythema, induration, edema, and ulcerations at the treatment site and are associated with higher rates of recurrences than treatment with surgical techniques [21].

Although topical fluorouracil has the potential to treat also subclinical disease in adjacent areas ("field therapy"), the discomfort associated to treatment may cause poor adherence to treatment in many patients. Recurrence after treatment with topical fluorouracil has been reported. In a small study comparing different treatment modalities in patients with actinic cheilitis involving >50 percent of the lower lip, recurrence was observed in 7 of 10 patients treated with topical fluorouracil after a follow-up time of 48 months or longer [22]. A randomized, vehicle-controlled trials evaluated the efficacy of 5-FU in the treatment of actinic chelitis, the rate of vehicle responders achieving total clearance of lesion was close to zero. The number of vehicle responders reaching partial clearance, however, was much higher with treatment responses ranging from 21.6 to 34.4%. The vehicle responses observed in topical 5-FU trials appear to corroborate those in efficacy evaluations of other topical actinic keratosis treatments [23].

Topical imiquimod may be an alternative topical treatment for multifocal or diffuse mild to moderate actinic cheilitis. Imiquimod 5% cream is applied to the involved area three times per week for four to six weeks. In a series of 15 patients with actinic cheilitis treated with topical imiquimod, all patients showed clinical clearing four weeks after discontinuing treatment [24]. One efficacy evaluation of 5% imiquimod cream as compared with its vehicle showed a median reduction of lesions of 86.6% in the imiquimod-treated group and 14.3% for the vehicle-treated group [25]. Another efficacy investigation of 5% imiquimod cream compared with its vehicle, both applied 3 days a week for either 1 or 2 weeks, reported a 61% partial reduction of lesions in the active drug group versus a 25.2% partial reduction in the vehicle group [26]. Adverse effects of topical application of imiquimod included erythema, induration, erosions, and ulcerations.

The most commonly used topical retinoids are: tretinoin, adapalene, isotretinoin, tazarotene, retinol and retinaldehyde. Tretinoin, or all-trans retinoic acid, was introduced by Stuttgen in the treatment of skin diseases in 1959 (quoted in Torras, 1996). Francz, Conrad, & Biesalski in 1998 reported that topical tretinoin protects the skin against damage from UVA and UVB rays. Griffiths in 2001 reported that tretinoin facilitates the ability to prevent collagen loss and stimulate new collagen formation within the papillary dermis of sun-exposed skin. In a multicenter study, patients treated with topical tretinoin appeared to develop an increased awareness of the adverse effects of sun exposure and increased motivation to employ sunscreens and sun avoidance as additional means of preventing skin damage [27]. The action mechanism of retinoids in the prevention and treatment of skin cancers has not yet been fully elucidated. They are known to: have antiproliferative and anti-apoptotic properties; regulate the differentiation and growth of keratinocytes; interfere in the process of tumor initiation; reduce regulation of proto-oncogenes; increase the expression of p53 and pro-apoptotic caspases; and sensitize keratinocytes to apoptosis. In murine models of skin carcinogenesis, retinoids target the BRaf/ Mek/Erk signaling pathway. It is speculated that they have a role as an antioxidant, reducing the number of sunburn cells. They may act against the human papillomavirus (HPV), which is considered a co-carcinogen [28].

Diclofenac in hyaluronic acid gel has been employed in the topical treatment of actinic keratoses with satisfactory results and well-tolerated side effects by the majority of the patients. In addition, this treatment has the advantages of not being invasive, having low cost and showing few side effects and good aesthetic results. Actinic cheilitis is a lesion of the lip vermillion, analogous to actinic keratoses, which has been treated by surgical procedures and topical drugs, some with a cytotoxic effect and the potential to cause tissue destruction.

The topical action of diclofenac in a hyaluronic acid vehicle has been investigated for the treatment of actinic keratoses showing promising results and less intense adverse effects in comparison with other drugs such as 5-fluorouracil. Ulrich et al. & Nelson et al [29] in 2007 utilized diclofenac in the treatment of actinic chelitis, in samples of 6 and 19 individuals, respectively. Ulrich et al. utilized this drug for 6 weeks and Nelson et al in 2007 for

90 days. Diclofenac is a non steroidal anti-inflammatory agent (NSAID) whose mechanism of action is not completely understood. Its possible antineoplasic effect is being investigated, because it induces apoptosis by inhibiting cyclooxygenases (COX-1 and COX-2), which are involved in the metabolism of arachidonic acid and are super expressed in various epithelial tumors. The hypothesis proposed is that NSAIDs act by inhibiting the metabolism of arachidonic acid, impede the potent tumorigenic effects of its metabolites. Such effects include the conversion of pro-oncogenes to oncogenes, inhibition of immunologic vigilance, inhibition of apoptosis, stimulation of angiogenesis and increase in invasiveness of tumor cells. Therefore, diclofenac can be effective in the treatment as well as the prevention of epithelial lesions related to actinic radiation. Hyaluronic acid, the vehicle in which diclofenac is delivered, has been widely utilized in the cosmetics industry because of its moisturizing properties. This polysaccharide is chosen primarily because it allows the accumulation of diclofenac in the epidermis, prolonging its half-life at the site of action. In addition to these effects, Wolf, et al. in 2001 suggested that the hyaluronic acid gel may have intrinsic activity, increasing the efficacy of treatment. The local reactions including pruritis, erythema and/or burning sensation can be observed in some cases & can be tolerated by the patients. These adverse reactions have also been described by other authors who studied the use of diclofenac for the treatment of keratoses as well as actinic cheilitis [30]

Chloroquine has been used in the treatment of malaria from over 60 years and is commonly sold as an over-the-counter medication, used as an anti-inflammatory drug in the treatment of rheumatoid arthritis, discoid lupus erythematosus, and amoebic hepatitis. It was first synthesized in Germany by Bayer Corporation in 1934 as a cheaper alternative to the costly quinine, but was then considered toxic for any significant biological use. However, it gained popularity during World War II, as there was a demand for cheaper, readily available antimalarial drugs. Choloroquine was subsequently discovered to be more effective than the quinine or quinidine against intraerythrocytic malarial parasites. The multiple mechanisms of chloroquine action have been proved to be useful in the treatment of skin diseases such as, lupus erythematosus, dermatomyositis, porphyria cutanea tarda, and sarcoidosis. The lysosomotropic effects of chloroquine are widely believed to be responsible for its various properties in different diseases.

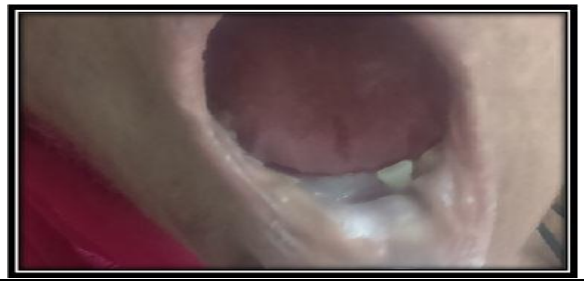
These drugs stabilize the lysosomal enzymes, inhibit the antigen-presenting cells, and stimulate T-lymphocyte, blocking the proinflammatory cytokine cascade and endosomal toll-like receptor signaling. It decreases the production of the pro-inflammatory cytokines IFN-γ, tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) in LPS- or phytohemagglutinin stimulated peripheral blood mononuclear cells, and also augmented LPS-induced expression of TNF-α, IL-1α, IL-1β, and IL-6 in monocytic and microglial cells. Chloroquine induces, rather than inhibits, the production of pro-inflammatory cytokines in astroglial cells through activation of the transcription factor NF-κB, when administered alone [31].

It has been concluded that chloroquine could induce either anti-inflammatory or proinflammatory responses in the central nervous system (CNS) depending on the cellular context. It also exerts anti-inflammatory effects via nonlysosomotropic mechanisms.

Chloroquine inhibits TNF-α release in macrophages through inhibition of TNF-α mRNA synthesis, hence showing it can also disrupt gene transcription but does so without interfering with posttranslational modification or release of the cytokine from macrophages [32].

The most effective protection against sun damage is the use of **sun screens** and **lip balms** reducing sun exposure. Regardless of the treatment modality used, regular clinical follow-up is essential for actinic cheilitis. A few straight forward precautions must be introduced in childhood itself and continued throughout to prevent the disease. The basic precautions include: Avoid outdoor activities during peak sunlight hours; wearing of protective clothing covering during the outdoor activity and of a wide-brimmed hat for the face and lips; and the liberal and daily application of an effective sunscreen preparation. Further treatment choices will depend on the nature and extent of the disease and other patient considerations.

Figure 1. Actinic keratosis on mandibular lip Courtesy: Outpatient Department of Oral Medicine, Radiology & Diagnosis, Institute of Dental Education & Advance studies



CONCLUSION

Any lip lesion, even though it appears benign, should prompt the clinician to perform a biopsy, to identify any dysplastic changes and prevent further morbidity or mortality. The predisposition of other family members to these actinic changes must be considered, and also, there is a scope for genetic studies in these patients. Appropriate and timely treatment of actinic chelitis is necessary to prevent malignant transformation into invasive squamous cell carcinoma of the lip.

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