J Oral Med Oral Surg 2023;29:30
https://doi.org/10.1051/mbcb/2023029

https://www.jomos.org

JOMOS
Journal of Oral Medicine and Oral Surgery

Educational Article

Actinic cheilitis: guidance on monitoring and management in primary care

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(Received: 13 July 2023, accepted: 17 July 2023)

Keywords: Actinic cheilitis / ultraviolet rays / lip squamous cell carcinoma

Abstract – Actinic cheilitis is an oral potentially malignant disorder caused by UV radiation leading to damage to epithelial keratinocytes of the lips. It predominantly affects the vermillion border of the lower lip. Due to its association with chronic UV exposure, associated risk factors include geographic areas, outdoor occupations, and skin subtypes. A high proportion of lip squamous cell carcinomas arise from actinic cheilitis lesions, with histological examination usually showing a degree of dysplasia. This paper aims to review the existing literature regarding the clinical picture of actinic cheilitis, its prevalence, differential diagnoses, and consensus on management, for the education of the general dental practitioner in identifying and surveillance of this lesion.

Introduction

Actinic cheilitis (AC) is classified as an oral potentially malignant disorder by the WHO 2020 Collaborating Centre for Oral Cancer Workshop. It was first described in 1923 as solar-induced chronic inflammatory disorder of the lips [1]. It has a broad range of clinical presentation from dryness to white plaques, to atrophic and erosive areas of the lips [2,3]. There is a paucity of literature pertaining to AC published within Europe, and particularly the United Kingdom. General Dental Practitioners (GDPs) who are in ideal positions to identify these lesions, may not be aware of their presentations and associated risks. There is also little guidance on how patients diagnosed with AC should be reviewed within primary and secondary care settings. Given that a large proportion of squamous cell carcinomas of the lip develop on a background of AC [4], there have been attempts to improve early detection and education of susceptible groups, to facilitate early diagnosis and treatment to reduce the risk of invasive squamous cell carcinoma (SCCs) [5].

The objective of this paper is to provide the GDP with a comprehensive understanding of actinic cheilitis, its clinical presentation and pathogenesis. Methods of screening and preventative advice in primary care, and the consensus on management methods of AC lesions are also discussed.

Methodology

A scientific literature search performed during January 1967 and June 2023,was done using several databases (Science Direct, Google Scholar, Scopus, and Pubmed). The literature search included the following topics: actinic keratosis (affecting the lips), actinic cheilitis and lip squamous cell

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carcinoma. Review articles linked to these topics contributed to the structure of the current review. Embracing a consensus mapping methodology, the overall management of Actinic cheilites was proposed by Guy's and St Thomas' institution team and then disseminated to other authors from the multiple Oral Surgery and Oral Medicine units in Europe. Consequently, the multiple principles were narrowed, reaching an overall consensus.

Background

Actinic cheilitis can be defined as intradermal proliferation of histologically atypical keratinocytes in an area of the lips that has been chronically damaged by ultraviolet (UV) light [6]. It most commonly affects the lower lip and may present in several ways from innocuous blurring or wrinkling of the vermillion border and faint white patches (Figs. 1 and 2), to crusting or scaly, flaky keratotic patches.

Atrophy, erythema and swelling of the lips may also be seen. The white appearance is due to hyperkeratosis, while the red colour is caused by vascular shine-through when atrophy and erosions have occurred [7]. The lesions can be localised or diffuse. They are often asymptomatic. On palpation, there may be a fine sandpaper texture and the patient may experience persistent areas of dryness or a sensation of tightness and inelasticity of the lips [8]. Ulceration may suggest the presence of malignant changes (Figs. 3 and 4).

Risk factors

Geographical factors

There is a correlation with AC and UV exposure. Frequency can be seen to increase in geographical areas with higher UV rays, such as areas closer to the equator, high altitude, low cloud cover, low levels of ozone and areas with reflective surfaces such as water, sand, and snow [9].

Occupational and social factors

AC is also known as 'sailor's lip' or 'farmer's lip' due to its association with outdoor workers, particularly in those who have been working outdoors for over 25 years [10]. Some studies estimate this to be a 2-to-3-fold risk in this population [11], with the bulk of cohort studies having been conducted in populations engaged in sun-exposed work such as fishermen, farmers, construction workers and lifeguards [10].

Other correlated links to AC, include lower educational levels and socio-economic status, poor diet, and low prioritisation of self-care habits such as the use of sun protective factor (SPF), cosmetic products and protective clothing.

Phenotype

AC is frequently linked to individuals with Fitzpatrick skin types 1 and 2 [12], skin types that burn easily, never tans or tans minimally, and sensitive to UV exposure. Other associated physical features may include blonde or red hair, and blue, green, or grey eyes.

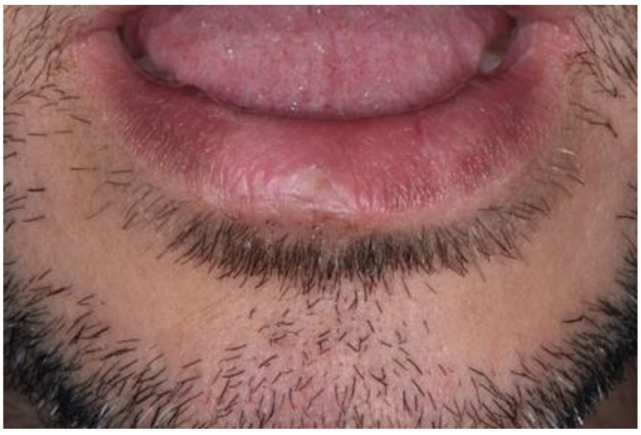

Fig. 1. Actinic cheilitis affecting the lower lip with pallor and blurring of the vermilion border.

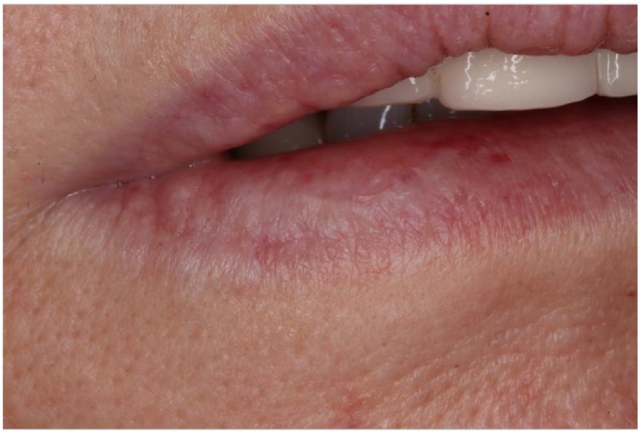

Fig. 2. Actinic cheilitis affecting the lower lip with pallor and blurring of the vermilion border.

Age and sex

AC is most likely to affect older males [11,12].

Medical history

A history of non-melanoma skin cancers is also a risk factor for AC. Individuals who have medical conditions such as albinism and xeroderma pigmentosum are also at increased risk, due to the absence of melanin as a protective factor in absorbing UV radiation, and inability to repair DNA damage caused by UV radiation respectively [12]. A study of an albino population in Togo, West Africa demonstrated the presence of actinic cheilitis in 50% of this cohort [13].

Prevalence

Figures on the incidence of actinic cheilitis in England and Europe are limited, as most studies were conducted in countries with higher sun exposure. Cohort studies of sun-exposed populations (*e.g.*, miners, farmers, fishermen and

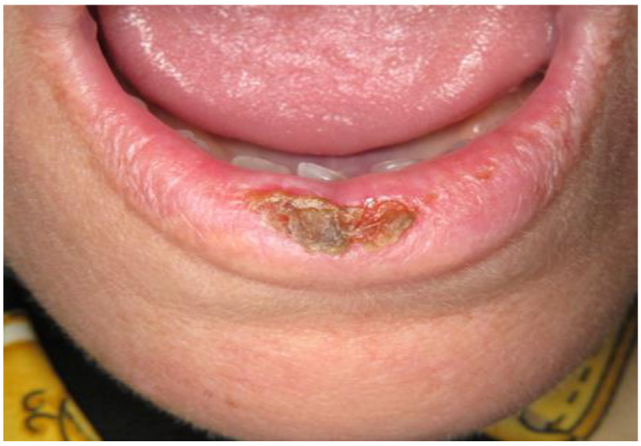

Fig. 3. Squamous carcinoma arising in the midline of the lower lip.

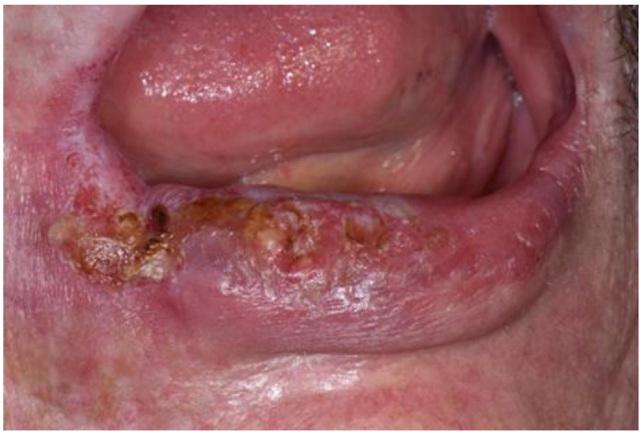

Fig. 4. Squamous carcinoma arising in the midline of the lower lip.

beach workers) reported a prevalence rate of between 8.5% to 39.6% [14–20]. Prevalence within the general population appears to be lower, between 0.3% and 3.7% [21,22]. However, a study in Spain reported the presence of actinic cheilitis in 31.3% of the population aged over 45 years [23]. Overall, it is difficult to determine accurately the prevalence of AC within populations due to varying demographic factors across these low-quality studies, as well as variety in data collection methods, such as through histological or clinical diagnosis.

Diagnosis

Diagnosis is made clinically, particularly by inspection and palpation of lesions, in the context of the patient's medical and social history, and oral cavity. However, an incisional biopsy can confirm the diagnosis histologically, and exclude severe dysplasia or lip squamous cell carcinoma [3,5].

Histological signs of actinic cheilitis include hyperkeratosis of the epithelium, as well as possible hyperplasia and epithelial atrophy. In the connective tissue layer, the presence of solar elastosis can be seen [8]. This refers to the basophilic degeneration of collagen fibres secondary to ultraviolet damage (Fig. 5). Other common features seen include the presence of generalised vasodilation, inflammation, and the presence of plasma cells, lymphocytes, and other white blood cells [24,25].

Differential diagnosis

There are several conditions affecting the lips that may have similar clinical presentations to AC. We present below some of the common conditions with further guidance of how General Dental Practitioners can distinguish them from AC.

Chapped lips

Sometimes referred to as cheilitis simplex, the lips may undergo cracking, fissuring and/or desquamation secondary to a lip-licking habit. This may be exacerbated by the presence of cold and windy environmental conditions. Cheilitis simplex, unlike actinic cheilitis, is a common condition and usually reversible in its nature [26]. It is managed by habit-breaking and topical application of lip balms and emollients.

Exfoliative cheilitis

Exfoliative cheilitis is characterised by continuous peeling of the lips due to excessive keratin production in lip tissues. The lips usually develop a thickened surface, which may thicken to form a yellow crust. Removal of the crust may show underlying erythema, bleeding, and formation of a haemorrhagic crust, which usually occurs in a cyclical manner, and may be associated with secondary infection [26]. Exfoliative cheilitis tends to be more common in a younger age group and linked to psychiatric disorders and factitious behaviours [27]. Underlying infection should be treated with the appropriate antimicrobials (*i.e.*, miconazole gel, fusidic acid). Topical calcineurin inhibitors and lip emollients may be used to prevent recurrence, although there have been case reports of invasive treatment using laser, cryotherapy, and electrocautery [26,28].

Herpes labialis

Herpes labialis, or cold sores, occurs due to the recrudescence of herpes simplex virus (HSV) from nerve ganglions following primary infection. Triggers include immunosuppression such as sunlight, menstruation, and upper respiratory tract infections. Clinically it commonly presents as multiple 1–2 mm vesicles on the lip which coalesce, accompanied by symptoms of burning. Diagnosis is usually made clinically, but this may be confirmed with a viral swab. Prompt treatment with oral or topical antivirals shorten the duration of eruptions and symptoms [29].

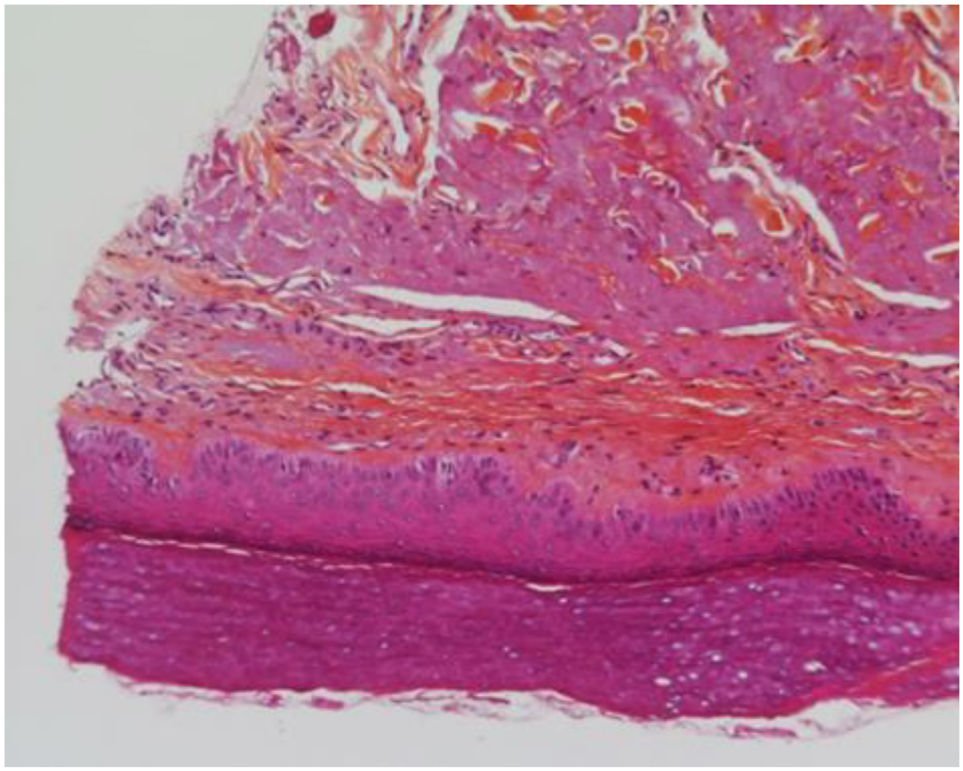

Fig. 5. Elastosis seen in actinic cheilitis.

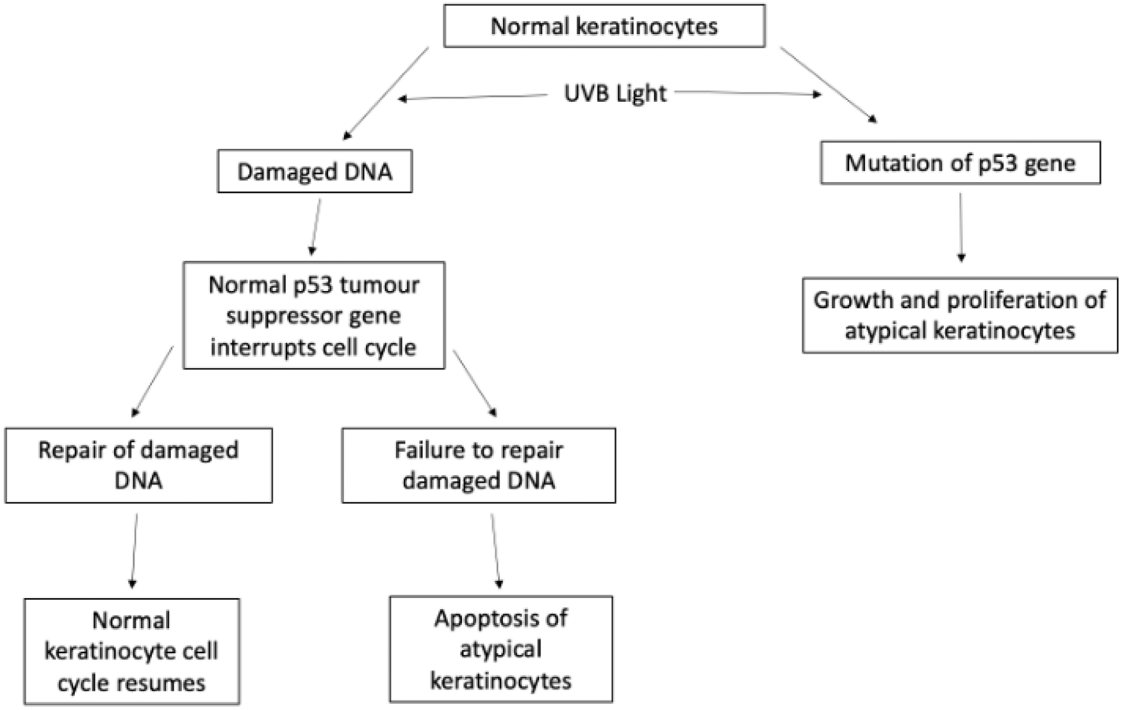

Fig. 6. Effect of UVB light on the keratinocyte cell cycle adapted from Wood *et al.* [8].

Oral lichen planus

Oral lichen planus affecting the lips in isolation is rare. Numerous case reports document that patients typically present with the atrophic subtype, with erosions and crusting of the lips [30], more commonly with other intraoral sites being affected as well. Diagnosis is made through histological examination and treated using topical corticosteroids [31]. Oral lichen planus is also a potentially malignant disorder which requires routine monitoring.

Pemphigus vulgaris

Pemphigus vulgaris is an immunobullous condition, which may manifest as erosions involving the lip. The oral mucosa is typically involved as well, and extra-oral sites such as the genitals, eyes and skin. Diagnosis is more complex, requiring histology and immunofluorescence studies [26]. Treatment usually involves a combination of topical and systemic corticosteroids, and immunosuppressants.

Erythema multiforme

Erythema multiforme (EM) is a hypersensitivity reaction with mucosal and cutaneous involvement. HSV-1 and HSV-2 are most implicated. Other causes include pneumonia-causing bacteria, drugs such as NSAIDs or are of idiopathic origin. EM typically presents as erosion of the lips and oral mucosa, often with the development of haemorrhagic crusts. Other sites include the skin, genital and ocular mucous membranes. Diagnosis is by histological and immunofluorescence studies. Treatment includes the use of topical and systemic corticosteroids in the acute phase. Long-term antiviral drugs may be considered in the prevention of recurrence if the aetiology is known to be HSV [32].

Keratoacanthoma

Keratoacanthomas are benign epithelial tumours that arise from hair follicles in sun-exposed parts of the body including the lips, usually at the vermillion border. They present as dome-shaped lesions with a central crater or keratin plug. They may appear clinically like squamous cell carcinomas, and differentiation arises from histological analysis. The most common treatment modality is complete excision as this allows for histological examination of the lesion in its entirety [33].

Lip squamous cell carcinoma

Approximately 95% of lip SCCs arise from pre-existing AC lesions [2]. Ulceration or induration are suspicious features which may suggest the presence of squamous cell carcinoma and areas of concern should be biopsied to gain histopathological diagnosis.

Pathogenesis

AC occurs due to chronic exposure to sunlight. The wavelength of ultraviolet light can be classified into UVA (320-400 nm), UVB (290–320 nm) and UVC (100–290 nm). UVB radiation is the primary cause of actinic damage, with 70% being absorbed by the skin [34–36]. UVB radiation causes thymine dimer formation in DNA and RNA, as well as production of 6–4 pyrimidine photoproducts and substitutions of cytosine–thymine (C–T) DNA [11], which leads particularly to mutations of p53. As seen in Figure 6, this leads to growth and proliferation of atypical keratinocytes [8,11,37], as normally p53 would trigger apoptosis of premalignant and malignant keratinocytes to prevent clonal expansion.

The lips are more susceptible to this UV damage due to its thinner epithelium and keratin layer, fewer sebaceous glands and lesser melanin compared to cutaneous epithelium [35,36,38].

Apart from UV radiation, human papillomavirus (HPV), particularly of the beta and gamma types have been implicated in actinic keratosis and SCC [39]. Although the molecular mechanism of their role in the development of SCC is not well understood, one study postulates the roles of HPV and UV radiation as co-factors in promoting cellular mutations [40,41].

Actinic cheilitis and lip squamous cell carcinoma

AC is considered an oral potentially malignant disorder. Studies involving actinic keratosis (actinic damage to the skin) show that genes upregulated in actinic keratosis and squamous cell carcinomas were downregulated in normal skin, and vice versa [42]. The finding that similar differentially expressed genes in both actinic keratosis and squamous cell carcinomas, and the close genetic relationship of these two conditions, supports the idea that actinic keratosis, and in turn AC, is a precursor lesion of squamous cell carcinoma [43].

The few histologic studies of AC have shown evidence of dysplasia in all cases [1,24]. However, the degree of dysplasia and presence of solar elastosis did not correlate to the risk of malignant transformation, nor are predictors for progression to squamous cell carcinomas. The only histologic feature shown to be significantly associated with the presence of invasive SCC and epithelial atypia was the intensity of inflammatory infiltrate seen in histologic slides [44].

Figures on the malignant transformation rate of actinic cheilitis have previously been estimated to be 6–10% by Crane and Muse [10] and 10–30% in several other articles without substantial evidence [2,45]. However, to date, there is only one article in a systematic review demonstrating this to be 3.07% [25,38]. Therefore, a greater number of high-quality studies are needed in this area.

Management

Treatment approaches include prevention, non-surgical therapy, and surgical therapy [46]. These therapies aim to reduce the risk of malignant transformation while preserving aesthetics and function. Evidence suggests that results are improved when non-surgical pharmacological therapy is used in tandem with surgical approaches [47].

The 2022 Oral Potentially Malignant Disorders Healthcare Professional Training guidelines outlines that treatment approaches should be based on the extent of lesions and severity of dysplasia. Topical pharmacological methods are favoured up to mild dysplasia, although some mildly dysplastic lesions may be amenable to surgical management. Excision or vermilionectomy are indicated for moderate to severely dysplastic lesions. All patients should be provided preventive advice regardless of severity of dysplasia [48].

Prevention

Prevention of actinic cheilitis includes reducing exposure to sunlight by using sun protective factor on the skin and lips, protective clothing (such as a wide-brimmed hat with UV protection) and reduced outdoor activities when UV radiation is at its peak [8]. Generally, smoking cessation and alcohol reduction advice should be provided in line with the Very Brief Advice on Smoking for Dental Patients by the National Centre for Smoking Cessation and Training (NCSCT), due to the well-established link between smoking, alcohol, and cancer [49].

Non-surgical therapy

5-Fluorouracil with trichloroacetic acid

5-Fluorouracil (FU or 5FU) is a cream-based chemotherapy medication. It is a pyrimidine base analogue that inhibits the thymidylate synthetase enzyme, which is involved in the synthesis of DNA and RNA, thereby particularly targeting neoplastic cells due to their increased metabolic activity. 5FU may be used alongside trichloroacetic acid (TCA), which is a chemical peel that causes sloughing of epidermal and superficial dermal cells [50]. This combination therapy rate demonstrates a recurrence rate of 50–70% within 4 years [29]. The BNF recommends a twice daily application for 3–4 weeks as the initial regime. Poor compliance is common due to painful side effects such as erythema, erosions and ulcerations which are worsened by exposure to sunlight [50]. Thus, concurrent use of SPF is recommended.

Imiquimod

Imiquimod (*Zyclara* 3.75% or *Aldara* 5% cream) is an immune modulator. It binds to toll-like receptor 7 which can enhance the release of certain cytokines which can act as pro-inflammatory agents to lead to apoptosis of abnormal cells [50]. It is rubbed into affected areas between once daily to several times a week and left on affected areas for 8 hours before being rinsed off.

Photodynamic therapy

Photodynamic therapy involves the application of topical photosensitising agents to affected areas in combination with a light source to induce radical oxygen species which affect cell membranes and lead to cell death of cancer cells. The photosensitising agent used is typically 5-aminolevulinic acid [50]. Common side effects include a burning or tingling sensation, erythema, crusting and swelling of the site. Patients are also advised to use SPF and to avoid direct and indirect sunlight for 48 hours after treatment. However, it is generally well tolerated by patients and provides a good cosmetic outcome [8].

Surgical therapy

CO_2 laser

CO2 laser creates infrared light between 10 and 600 nm, producing a thermal effect and causing ablation of the targeted tissues. The aim of treatment is to vaporise the layer of epithelium. It can cause temporary eating difficulties, bleeding, and oedema [10]. It tends to be the treatment of choice for diffuse AC lesions with mild dysplasia [1,44,50].

Cryotherapy

Cryotherapy works by forming ice crystallisation intra- and extracellularly which causes damage to cells through vascular stasis and apoptosis [36]. It can cause oedema, pain, scarring and hypo- or hyperpigmentation [50].

Vermilionectomy

Vermilionectomy is the removal of the full thickness of the lip epithelium. Primary closure is achieved with a labial mucosal flap [50]. This procedure has a low recurrence rate and more than 80% of patients obtain complete resolution of their lesions [10]. Side effects include bruising, swelling, temporary eating difficulties, paraesthesia, and necrosis [10]. This treatment option is usually considered in actinic cheilitis showing moderate to severe dysplasia.

Review of treatment efficacy

A prospective study of 40 patients by Robinson from 1989, showed no recurrence of the lesion after 4 years when treated by CO_2 laser or vermilionectomy [34]. A review of these various therapies by Shah *et al.* compared the initially apparent clinical efficacy of different treatment options. This showed that surgical vermilionectomy and CO_2 laser were the most successful treatment options for actinic cheilitis, while TCA chemical peel alone was the least effective [50].

Overall recommendations

It is important to be aware of AC, as it is a potentially malignant disorder with potential to develop into lip SCCs. Lip SCCs account for a third of oral cancers, of which 95% arise

from pre-existing actinic cheilitis lesions [40]. Its prevalence varies but main risk factors include sun-exposure and age. There is limited information on its malignant transformation rate.

GDPs, particularly in countries with high sun exposure, should examine the lips as part of routine dental examinations. It may be prudent to inquire about lip symptoms, the patient's occupation, and hobbies as part of the history taking process. GDPs should also be equipped with a good knowledge on preventive self-care advice, as well as smoking cessation advice, reduction of alcohol consumption or reduction of other modifiable risk factors. If actinic cheilitis (or other premalignant conditions) are suspected, GDPs should readily refer these patients to local dermatology, oral medicine, or oral and maxillofacial surgery departments.

Within secondary care, actinic cheilitis is diagnosed clinically and through histopathological exam. The Oral Potentially Malignant Disorders Healthcare Professional Training guidelines, which outlines expert opinion throughout Europe, recommends 6-monthly reviews in the first 2 years, followed by annual review from the third year. Re-biopsies and reduction of review intervals are recommended if clinical changes are noted [48]. GDPs should likewise organise 6-monthly reviews for soft tissue changes, ideally between the patient's secondary care reviews, which will result in the monitoring of the patient by a dental professional every 3 months.

Conclusion

Diagnosing actinic cheilitis can be challenging due to its varying clinical presentations. A high degree of suspicion is needed, especially in high-risk groups. GDPs should regularly examine and document their extraoral findings involving the lips, and if there are any concerns about actinic cheilitis, referral to secondary care should be carried out for further examination, investigation, and management.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

This research did not receive any specific funding.

Ethical approval

Ethical approval was not required.

Informed consent

This article does not contain any studies involving human subjects.

Author's contribution

P. Shah: Writing original draft, Q. Feng: Writing original draft, B. Carey: drafting of manuscript, reviewing and editing, M. Diniz-Freitas: Writing original draft, J. Limeres: Writing original draft, L. Monteiro: Writing original draft, L. Silva: Writing original draft, J-C. Fricain: Writing original draft, S. Catros: Writing original draft, M. Fenelon: Writing original draft, N. Lombardi: Writing original draft, A. Pispero: Writing original draft, G. Lodi: Writing original draft, V. Brailo: Writing original draft, D. Vidovi Juras: Writing original draft, J. López-López: Writing original draft, R. Albuquerque: Conceptualization, drafting of manuscript, reviewing and editing.

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