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Treatment of actinic keratoses – be sure first

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Key points

- Actinic keratoses (AKs) are extremely common – about 60% of Caucasians in Australia will have at least one by the age of 40 years.
- They are localised proliferations of aberrant keratinocytes that develop most often from prolonged exposure to UV radiation but also as a result of immunosuppression, human papillomavirus infection and arsenic exposure.
- AKs may develop into squamous cell carcinomas (SCCs), and therefore are strong predictors of the subsequent development of nonmelanoma skin cancers.
- If thickening, bleeding or tenderness are present in an AK, malignancy should be excluded before treatment is commenced.
- Patients at high risk of SCC should have their AKs biopsied if there is any doubt about the diagnosis.
- The most commonly used management options for removal are cryotherapy and 5-fluorouracil cream.

Actinic keratoses are clinically important because they have the potential to develop into squamous cell carcinomas. Treatment is aimed at preventing this transformation and at symptomatic and cosmetic improvement.

Actinic keratoses (AKs), which are also known as solar keratoses, are superficial cutaneous lesions consisting of localised proliferations of aberrant keratinocytes. They develop most commonly as a consequence of prolonged exposure to ultraviolet (UV) radiation.

AKs are clinically important because they are considered premalignant lesions with the potential to develop into squamous cell carcinomas (SCCs). They therefore represent strong predictors of the subsequent development of nonmelanoma skin cancers.

EPIDEMIOLOGY AND NATURAL HISTORY

The most important aetiological factors in the development of AKs are cumulative ultraviolet (UV) radiation exposure (including tanning bed use) and individual susceptibility. Individual susceptibility factors include increasing age and phenotypical characteristics, such as fair skin that burns easily and tans poorly, blue eyes and red or blond hair.[1] Other risk factors for the development of AKs include chronic immunosuppression (for example, in organ transplant recipients), human papillomavirus infection and exposure to arsenic.[2,3]

Signature UVB-induced DNA mutations at the tumour suppressor gene p53 (cytosine to thymine substitution in the presence of adjacent pyrimidine) are found in cells in AKs. They provide molecular evidence supporting the role of UV radiation in the development of these lesions.[4]

The prevalence of AKs in the Caucasian population in Australia is 40 to 60%,[5] as compared with 11 to 25% in the USA[6] and 6 to 15% in northern England.[7] In Australia, it has

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been estimated that 60% of Caucasian individuals aged 40 years or older will have at least one AK lesion.[8]

AKs are considered precancerous lesions as most SCCs are associated with adjacent or contiguous AKs.[9] Most SCCs developing in one monitored population arose within pre-existing AKs.[10] Some authors consider AKs to represent incipient intraepidermal carcinomas, but the potential for the malignant transformation of AKs to SCCs is not exactly known; reported rates range from 0.025% to 16% per year.[10,11] In addition, AKs may spontaneously regress at a rate reported in the order of 15 to 25% over a one-year period.[12,13]

CLINICAL PRESENTATION

The presentation of AKs is typically that of erythematous scaly macules or papules that are 2 to 6 mm in diameter. The lesions may be discrete or confluent, forming plaques.

Classically, AKs are more easily felt than seen, but they may also present as variants that are thickened or hypertrophic, associated with a cutaneous horn, or pigmented. They occur predominantly on chronically sun-exposed skin, such as the head and neck, forearms and dorsa of hands (Figures 1 and 2). Although they are largely asymptomatic, they may be pruritic, burning or stinging and can also bleed or crust.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSES

Histopathologically, AKs are characterised by foci of atypical, pleomorphic keratinocytes along the basal layer of the epidermis, with sparing over the adnexal structures. The diagnosis of AK is regularly made clinically without a biopsy. However, it is important to bear in mind that clinical diagnostic accuracy among dermatologists has been reported to be as low as 74% and that 83% of the lesions inaccurately diagnosed as AKs were actually some form of skin cancer.[14] In light of this, the threshold for biopsy should be lower in high-risk patients.

The differential diagnoses of classic erythematous AK, hypertrophic AK and pigmented AK are listed in Table 1.

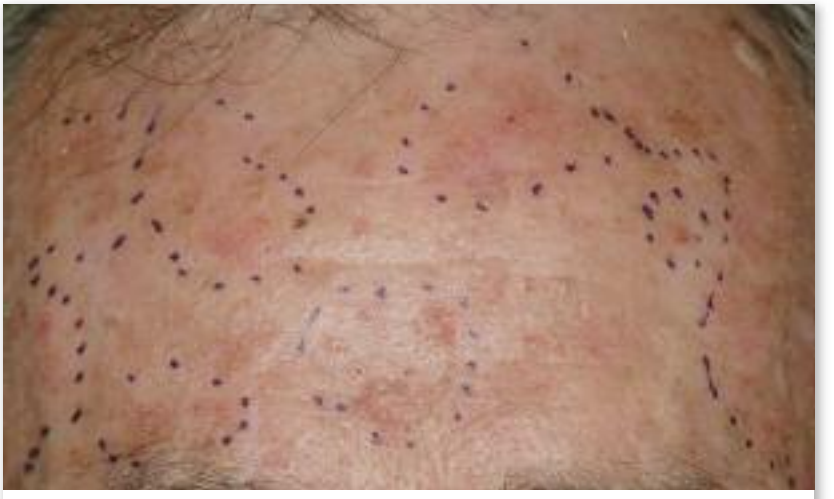

Figure 1. Actinic keratoses on the scalp. Prolonged sun exposure is the major cause of these superficial cutaneous lesions.

MANAGEMENT

Given that the rate of malignant transformation of AKs is not exactly known, some clinicians feel that definitive treatment of AKs is not universally required solely on the basis of preventing progression to SCCs. However, as 3 to 4% of SCCs will metastasise, other clinicians advocate early treatment of AKs to avoid the need for more extensive treatment in the future.[15]

Treatment should certainly be discussed if AKs are causing symptoms or disfigurement. If features such as thickening, bleeding or tenderness are present, a biopsy should be performed of the thickest area prior to treatment to exclude malignancy. It is likely that repeated treatments would be required at intervals, as new AKs tend to develop over time.

Treatment options are discussed below and listed in Table 2.

Topical treatments

Emollients

In one study where emollients were employed as the placebo arm, resolution of AKs was seen in up to 34% of patients after 60 days of use.[16] It is, however, likely that emollients reduce the clinical manifestations of AKs rather than reverse the biological processes.

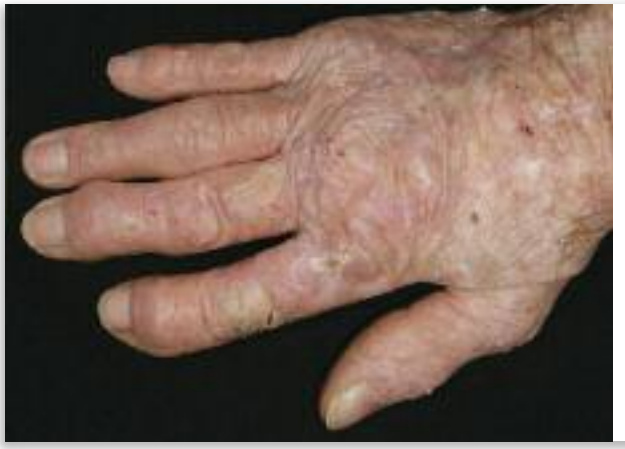

Figure 2. Actinic keratoses on the hand in a transplant recipient. Chronic immunosupression is a risk factor for the development of these lesions.

TABLE 1. THE DIFFERENTIAL DIAGNOSES OF ACTINIC KERATOSES

Erythematous actinic keratoses
- Irritated seborrhoeic keratosis
- Lichenoid keratosis
- Squamous cell carcinoma *in situ* (Bowen's disease, intraepidermal carcinoma)
- Superficial basal cell carcinoma
- Psoriasis

Hypertrophic actinic keratoses
- Squamous cell carcinoma
- Discoid lupus erythematosus
- Porokeratosis
- Verruca vulgaris

Pigmented actinic keratoses
- Solar lentigo
- Flat or macular seborrhoeic keratosis
- Lentigo maligna

Sunscreens

Sunscreens have a combined emollient and photoprotective effect on AKs. Sunscreen use has been shown to decrease UVB-induced p53 mutations as well as UV-induced immunosuppressive effects.[17]

In a study carried out in Queensland, a single daily application of sunscreen (sun protection factor 16) was associated with a 24% reduction in AK development over a two-year period, compared with discretionary use of the same sunscreen.[18] A shorter study found resolution of 24.6% of clinically diagnosed AKs over a six-month period with daily sunscreen application (sun protection factor 17).[19]

Salicylic acid

Salicylic acid preparations act primarily as emollients for mild AKs, but also provide a small additional benefit based on the keratolytic effects. A common formulation is 2 to 5% salicylic acid in sorbolene. Salicylic acid may also be used to prepare the treatment area prior to the application of topical 5-fluorouracil (5-FU) cream or photodynamic therapy (PDT) in order to reduce overlying keratin.

Diclofenac gel

Diclofenac 3% in 2.5% hyaluronan gel is considered to be a treatment with moderate efficacy and is used primarily to treat mild AKs. Topical diclofenac is generally well tolerated and side effects consist mainly of pruritus and rash.

The mechanism of action of diclofenac, an NSAID, in the treatment of AKs is not well understood but may be related to the countering of the increased prostaglandin levels in AK lesions through inhibition of inducible cyclo-oxygenase (with preferential COX-2 selectivity over COX-1), and hence inhibition of prostaglandin synthesis. Lipoxygenase is also inhibited. Diclofenac in hyaluronan gel induces apoptosis, inhibits cell proliferation and suppresses angiogenesis.

Two randomised, vehicle-controlled trials have demonstrated a significant difference in AK clearance following twice-daily treatment with diclofenac 3% gel. In one trial there was resolution of 70% of target lesions in the active arm after 60 days of treatment versus 34% in the control arm. In the other trial, 50% of patients in the active arm achieved a target lesion number score of zero after 90 days of treatment versus 20% in the control arm.[16,20]

It is recommended that diclofenac 3% in 2.5% hyaluronan gel be applied twice daily for 90 days. Cost is a potential limitation of the use of topical diclofenac in the treatment of AKs because the gel is not listed under the Pharmaceutical Benefits Scheme (PBS) for this indication.

5-Fluorouracil

5-FU is a cytotoxic agent that is selective for dysplastic keratinocytes. It acts by inhibiting thymidylate synthetase (which is needed for DNA synthesis) and possibly also by interfering with the formation and function of RNA. Cytotoxic metabolites formed intracellularly from 5-FU induce cell cycle arrest and apoptosis.

5-FU therapy has been a mainstay of topical treatment for AKs for over 30 years, with efficacy confirmed by a wide range of open trials and dose-ranging studies, as well as two randomised controlled trials. A trial of a three-week, twice daily application of 5-FU in the currently available formulation of a 5% cream showed a mean reduction of 78% of lesions on the face at 12 months.[21] A similar trial showed a mean reduction of 70% of lesions on the hands at six months.[22]

Many different treatment regimens have been proposed for topical 5-FU, but the standard regimen usually consists of a twice daily application to the entire affected region (field treatment) for two to four weeks. Treatment is usually ceased when the patient reaches certain clinical

TABLE 2. TREATMENT OPTIONS FOR ACTINIC KERATOSES

Topical treatments
- Emollients
- Sunscreens
- Salicylic acid 2 to 5%
- Diclofenac 3% in 2.5% hyaluronan gel twice daily for 90 days
- 5-Fluorouracil 5% twice daily for three weeks
- Imiquimod cream two to three times weekly for up to 16 weeks

Cryotherapy

Photodynamic therapy

Curettage and surgical excision

Other treatments
- Oral retinoids
- Topical retinoids
- Ablative lasers (carbon dioxide or erbium:YAG lasers)
- Dermabrasion
- Chemical peels (35% trichloroacetic acid)

'endpoints', such as change of skin colour to dusky red, widespread crust formation or increasing pruritus. Local adverse effects such as pruritus should be anticipated, with 90% of patients treated experiencing moderate to severe skin irritation.[23] Use of 5-FU may also uncover incipient AKs, and areas of skin where no AKs are visible can become inflamed during treatment.

To reduce the side effects of topical application of 5-FU, some clinicians reduce the frequency of dosing but increase the duration of application (for example, from daily application for three to four weeks to once- or twice-weekly application for three months). The evidence for the efficacy of such regimens is conflicting.

Imiquimod

Imiquimod is an immune-response modifier that stimulates the innate immune response by inducing the synthesis and release of cytokines via binding to the cell surface Toll-like receptor 7 on immune cells, resulting in direct antitumour effects. It also indirectly stimulates cell-mediated immunity, leading to further cytokine production. In Australia, imiquimod has been approved by the Therapeutic Goods Administration (TGA) for the treatment of AK, superficial BCC and genital and perianal warts.

The standard treatment regimen for AKs is imiquimod 5% cream applied on two to three days per week for up to 16 weeks. After one to two weeks of therapy, the treatment area may be expected to become erythematous, crusted or eroded. If the reaction is too severe, patients can interrupt treatment for one to two weeks before restarting therapy. Systemic adverse effects may occur with imiquimod use, including interferon-like side effects such as flu-like symptoms, headaches and myalgias.

Large multicentre randomised controlled trials have demonstrated imiquimod to be effective in clearing AKs in 48 to 57% of cases.[24,25] In addition, the clearance of AKs is more common in patients who develop intense application site reactions.[26] One study has reported treatment with imiquimod has a superior field effect and sustained 12-month clearance of a complete treatment field compared with treatment with cryotherapy or 5-FU (sustained clearance was 73% for imiquimod, compared with 4% and 33% for cryotherapy and 5-FU, respectively).[27]

A potential limitation in the use of imiquimod cream to treat AKs is cost, as it is not listed under the PBS for subsidy for this indication. Although superior in efficacy, imiquimod is more expense than 5-FU, gram for gram, by a factor of approximately 19.

Cryotherapy

Cryotherapy with liquid nitrogen (boiling point, -195.8°C) is traditionally the most common treatment for AKs because of its low cost, ease of application and efficacy. Although clearance rates of as high as 98.8% have been described,[28] more recent randomised comparison studies have reported somewhat lower overall complete clearance rates of lesions, ranging from 68% (single freeze–thaw cycle) to 75% (double freeze–thaw cycle).[29,30]

The recommended freeze time for the treatment of AKs is about 5 to 15 seconds, depending on the lesion thickness. Cryotherapy can cause considerable localised pain, particular in sensitive areas such as the head and neck, both during and following treatment. Cryotherapy also nonselectively destroys healthy tissue within the treatment field, and treatment is followed by erythema, swelling and occasionally blistering. Another significant potential complication of cryotherapy is hypopigmentation, as melanocytes are exquisitely sensitive to cold temperatures. Hypopigmentation occurred in 29% of cases in one report and appeared to be more likely with increasing freeze times.[31] Nevertheless, the cosmetic outcomes of cryotherapy are generally considered to be good to excellent.

Photodynamic therapy

PDT consists of the application of a pre-photosensitiser cream (5-aminolevulinic acid [5-ALA] or its methyl ester, methylaminolevulinate [MAL]), which is converted intracellularly via the haem biosynthetic pathway to photoactive porphyrins (predominantly protoporphyrin IX), followed by irradiation with a dedicated light source of 405 to 635 nm wavelength. The irradiation of the photoactive porphyrins in the presence of oxygen results in the production of reactive oxygen species (such as singlet oxygen and hydroxyl radicals) that cause cell death. Selective destruction of neoplastic cells by apoptosis and necrosis is achieved through the increased absorption of the photosensitising agent compared with the

absorption by normal keratinocytes.

PDT has been shown in randomised controlled trials to be as efficacious as cryotherapy in the treatment of AKs, with overall complete clearance rates ranging from 69 to 93% for PDT compared with 68% (single freeze–thaw cycle) to 75% (double freeze–thaw cycle) for cryotherapy.[27,29,30,32-34] The use of two MAL–PDT sessions one week apart compared with single treatment results in greater clearance rates for thicker lesions (84% *v.* 70%, respectively) but similar rates for thin lesions (89% *v.* 93%, respectively).[34] In these studies, cosmetic outcome was generally superior and patient preference was generally greater for PDT compared with cryotherapy.

When used on non-face or scalp areas, however, MAL-PDT was reportedly inferior in efficacy when compared with cryotherapy (the mean percentage reduction of lesion count being 78% for MAL-PDT and 88% for cryotherapy) but the cosmetic outcome was significantly better.[35]

As well as the better cosmetic outcome and being preferred by patients, another major advantage of PDT over some other field therapy methods is that it is delivered by the treating doctor and hence compliance is assured.

The use of PDT is potentially limited by cost because it is currently not listed on the PBS or Medicare Benefits Schedule for subsidy or reimbursement when used for the treatment of AK. Nevertheless, a recent study in Belgium showed that PDT was cost-effective in the treatment of AKs compared with cryotherapy over a one-year period (at 58 Euros [about A$80] per lesion), in line with previous economic modelling.[36] The requirement of a specialised light source for illumination of photosensitised sites also limits availability of this treatment modality.

Surgical treatments

Curettage and surgical excision are sometimes used in the treatment of AKs. No studies have examined the efficacy of these treatments but they are of particular value in determining the histopathological nature of atypical AKs unresponsive to other therapies, especially where invasive SCCs need to be excluded. Disadvantages of curettage and surgery include the need for a local anaesthetic injection and the possibility of infection and scarring.

Other treatments

Retinoids

Use of a retinoid normalises keratinisation and reduces the dysplasia of AKs. Oral retinoids (acitretin is used in Australia) are used in selected patients, such as organ transplant recipients, to reduce cutaneous carcinogenesis. However, their use may be limited by adverse effects such as cheilitis, excessive peeling, headaches and dyslipidaemia, as well as the potential for rebound flaring of carcinogenesis once treatment is ceased.

Topical retinoids such as adapalene and tretinoin have been shown to be effective in treating AKs in some patients but are not approved by the TGA for this use. A regimen of tretinoin 0.1% applied twice daily for 15 months resulted in a lesion response rate of 73%, compared with 40% for placebo.[37] Topical retinoids are generally well tolerated but mild local reactions, such as photosensitivity, peeling, erythema and dryness, may occur.

Ablative lasers

Carbon dioxide or erbium: YAG (erbium-doped yttrium aluminium garnet) lasers may be used to treat AKs.[38,39]

Dermabrasion

Dermabrasion may be an effective treatment for AKs, with one study showing 96% of patients remaining free of AKs at one year.[40]

Chemical peels

35% Trichloroacetic acid chemical peels have been found to have similar efficacy to 5-FU 5% in treating widespread facial AKs, with improvement sustained at 12 months.[21]

CONCLUSION

AKs are a common dermatological condition, particularly in Australia. Treatment is aimed at the prevention of transformation to SCCs, as well as symptomatic and cosmetic improvement. There are multiple treatment options, the most commonly used being cryotherapy and topical therapies (such as 5-FU cream). Other available effective treatments include PDT, diclofenac gel and imiquimod cream, but their use may be limited by cost. MT

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A list of references is available on request to the editorial office.

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Treatment of actinic keratoses

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