The majority of patients presenting with actinic keratosis should be adequately managed in primary care; however, constant updating of skills using the latest treatment options is necessary

(This module was facilitated by Dr Johnny Loughnane)

**SKIN CANCER IS THE MOST COMMON FORM** of cancer presenting in primary care. It is treatable and, provided early diagnosis is made, curable. Because of the impact of early diagnosis on prognosis, early recognition and prompt treatment or referral of suspicious lesions is essential.

There are three main types of skin cancer: basal cell carcinoma (BCC), which is more common than squamous cell carcinoma (SCC), which in turn is more common than malignant melanoma (MM). Non-melanoma skin cancer (NMSC) is a collective term for BCC and SCC.

### Actinic keratosis (AK)

 SCC accounts for 20% of NMSC. It is estimated that between 25-80% of SCCs arise from an actinic keratosis (AK). With an ageing population and an increasing awareness of the potential seriousness of skin cancer, GPs face an ever-increasing demand for diagnosis and treatment. Many treatment options are available and allow very satisfactory care for the majority of patients without the need for referral to secondary care. Indeed, it is certain that secondary care will not be able to cope with the ever-increasing clinical demand in this area of dermatology. This article aims to outline the aetiology, diagnosis and management of AK in primary care. New treatment options that are expected to be soon available will be outlined.

**What is actinic keratosis?**

AK is a squamous cell carcinoma confined to the epidermis, ie. SCC in situ. The outer epidermis layer of the skin is separated from the underlying dermis by a basement membrane at the dermo-epidermal junction. SCC is a malignancy of the epidermal keratinocytes.

Abnormal differentiation of keratinocytes leads to development of dysplasia. When dysplasia is confined to the epidermis it is termed SCC in situ. Clinically, SCC in situ is evident as AK or Bowen’s disease (BD).

In AK the dysplastic cells are located in the lower layers of the epidermis. In BD the dysplastic cells occupy the whole of the epidermis. In neither AK nor BD do dysplastic keratinocytes penetrate the basal membrane. When malignant cells penetrate the basal membrane to the underlying dermis, it is called invasive SCC. While many invasive SCCs develop from SCC in situ (AK or BD), not all do. Frequently, invasive SCC develops de novo. This tends to be more aggressive than SCC developing from SCC in situ.

### Causes of AK

- Ultraviolet light associated with chronic sun exposure is the most common cause
- PUVA and narrow-band UVB therapy
- Human papilloma-viruses act as co-carcinogens in the pathogenesis of AK
- Immunosuppression: organ transplantation, chronic lymphatic leukaemia
- Chronic scars: Marjolin’s ulcer
- Chronic inflammatory skin disease such as lichen sclerosus

### Risk factors for AK developing

- Skin type 1 or 2
- Male sex
- Older age
- Living at high altitude and low latitude
- Outdoor work and recreation
- Genetic disorders (xeroderma pigmentosum, epidermolysis bullosa)
- Immunodeficiency

As the main cause of AK is cumulative UV exposure, it presents mainly on exposed areas of the head and neck and dorsal surface of forearms and hands (see Figure 1). It is especially common in those with an outdoor occupation. In truck drivers with driving experience of more than 40 years, more AKs have been found on the driver side on the dorsal surfaces of hand and forearm. Up to 25% regress spontaneously if left alone, especially if sun avoidance is practised.
The majority of persisting AKs do not progress to invasive SCC. Our best estimate is that less than 0.1% progress.

Patients may find them unsightly and may worry about the risk of progression to invasive SCC.

Incidence of AK is increasing. In the UK, 34% of males and 18% of females over the age of 70 years have AKs.

Immunosuppression

High-risk AKs occur mainly in immunosuppressed patients. Organ-transplanted patients have a 250-fold higher risk of developing AKs and a 100-fold higher risk of developing invasive SCCs. Lesions appear two to four years after transplantation and increase in frequency thereafter.

Special care needs to be taken when patients are on immunosuppressive therapies such as azathioprine, ciclosporin, oral steroids, etc. One disease, often forgotten, that considerably heightens risk is chronic lymphatic leukaemia. These patients need constant reminding of the importance of sun avoidance and the regular use of sun creams. An AK may rapidly develop into an invasive SCC which may behave very aggressively and even cause death if not dealt with early.

Clinical

AKs are rarely symptomatic, although they may itch or become sore. They present as skin-coloured to reddish-brown scaly macules, papules or plaques on a red base. As a result of hyperkeratosis, their surface is often covered with superficial scales. Their clinical presentation depends on the amount of surface scaling present. AKs often start as erythematous patches representing an area of increased vascularity. There is little or no scale initially. With time the skin surface becomes slightly rough. This rough texture is key to diagnosing early lesions. They are better recognised by rubbing the skin than by inspection. Rubbing gives an impression of sandpaper.

Increasing amounts of scale gives a roughened surface. Scale is quite adherent. It is difficult and painful to pick off. When scale is removed, a hyperaemic base with bleeding points is revealed (see Figure 2). More thickened scale gives the appearance of a cutaneous horn. Cutaneous horns may be difficult to differentiate from early, invasive SCC. They are found on areas of skin extensively damaged by sunlight (see Figure 3). Surrounding skin shows the characteristic signs of dermatoheliosis (chronic sun damage) such as freckles and solar lentigines.

Variants of actinic keratosis

A continuum of clinical signs marks the progression from AK to SCC, with no distinct clinical boundaries between them. Therefore, there is no definite way to distinguish between an AK and an SCC without a biopsy. For most straightforward AKs diagnosed in primary care, no biopsy is needed. Features listed in Table 3 only suggest progression to SCC. Lesions thought to be AKs or those not responding to treatment may actually be SCCs.

Spreading pigmented AK may resemble a scaling lentigo, seborrhoeic keratosis, or melanoma.

Cutaneous horn is a hypertrophic AK that accumulates keratin to become a conical hyperkeratotic protuberance. Actinic cheilitis (AC) is the equivalent of AK on the lip (see Figure 4). It presents with erythema, dryness, scaling, atrophy and erosions. The lip has a rough feeling when rubbed. It is more common on the more sun-exposed lower lip.
lip and it is not unusual that the whole lip is involved. It is difficult to distinguish AC from SCC. SCCs of the lip have a higher metastatic rate than other cutaneous SCCs. If in any doubt biopsy or refer.

Field cancerisation

AKs commonly affect an entire field such as sun-exposed areas on the forehead or the back of the hand. This is termed field cancerisation (see Figure 5). Within the field, AKs will be clinically obvious. However, skin that appears clinically normal may have dysplastic cells within the epidermis. The concept of field cancerisation has led to the concept of field-directed therapy, i.e. treating the whole area where AKs are found, not just the individual, visible lesions.

Treatment

Because the risk of progression to carcinoma is so small, treatment is not indicated for all AKs. Reasons to treat include symptoms such as itch and soreness, cosmetic appearance, and patient worry about the risk of developing cancer. AKs presenting in immunocompromised patients have a high risk of progression to invasive SCC. AKs in this patient group should be biopsied prior to treatment, to outrule SCC. It is probably best that such patients are managed in specialist clinics.

Treatment options for AK are categorised as either field-targeted or lesion-targeted. Lesion-targeted therapies are directed at individual AKs, especially if hyperkeratotic. Field-targeted therapies are directed at multiple AKs and larger areas of sun-damaged skin, aiming to treat all dysplastic lesions in the field, both clinical and non-clinical (i.e. visible and non-visible). Most areas of AK are subclinical and therefore not visible.

Lesion-targeted and field-targeted therapies may be combined, i.e. lesion-directed therapy to the thick AKs in an area with field-directed therapy to the remaining skin in the field.

Sunscreens

Sunscreens, if regularly applied, prevent the development of AKs and promote spontaneous regression in existing ones. Sunscreens that block both UVA and UVB ultraviolet light should be used. They should be applied to the face, lower lip, ears, neck, and backs of the hands and forearms in a thick layer. Most patients apply sunscreens too thinly, making them proportionally less effective. Those with bald heads should wear a hat to protect the scalp and ears. Patients should avoid being out in the sun when the shadow cast by one’s body is less than one’s height.

Treatmente of actinic keratosis in primary care

Treatment of AK in primary care includes cryosurgery, curettage, diclofenac in hyaluron gel (Solaraze), 5-fluorouracil or 5FU (Efudix) and imiquimod (Aldara).

Cryosurgery

Cryosurgery is the treatment of choice for lesion-directed therapy. Liquid nitrogen, delivered by spray or probe technique, is most effective. Using a cotton bud to apply liquid nitrogen is just as effective for all but thicker AKs. Cure rates up to 98% are achieved. It is quick and easy to learn, and safe when used appropriately. As there is no histology to confirm the diagnosis, one must be certain of the diagnosis before treating. If there is doubt, one should biopsy the lesion or refer for another opinion. Usually only one or two treatment sessions are needed. Cryotherapy should not be used on pigmented skin types as there is a significant risk of hypopigmentation.

Patients should be warned of the risk of pain and blistering. Sometimes crusting or a small ulcer may form following cryosurgery.

Thin AKs require a five to 10-second freeze. The lesion and a 2mm rim around it should be frozen as dysplastic cells are present beyond the visible border of the lesion. Timing starts once the freeze has reached the edge of this 2mm rim. Some cryosurgeons allow a thaw and repeat the freeze; however, one freeze is as effective as a double freeze. More hypertrophic or hyperkeratotic AKs should get a 15-20 second freeze, as keratin acts as an insulator. If using a cotton bud, moderate pressure should be applied.

Curettage

Not many GPs perform curettage, which is a pity as it is easy to learn, has the advantage of giving tissue for histology and gives excellent cosmetic results. It is particularly suited for hyperkeratotic AKs and lesions that have not responded to other treatment modalities or where you would like to be certain of histology. Cautery is not needed. Haemostasis is easily achieved using a tightly applied dressing (usually a simple plaster) once adrenaline is combined with the local anaesthetic.

5-fluorouracil

5-fluorouracil (5FU) is available as a 5% cream and is thought to work a direct cytotoxic effect on malignant cells. It is 90% effective. Hyperkeratotic AKs do not respond as well. It frequently causes considerable inflammation, especially on thicker lesions. It may be best to remove these surgically before starting topical 5-fluorouracil. It is licensed for twice-daily use for four weeks. Best results are obtained when it is applied to all of the area being treated. This allows treatment of subclinical lesions, but will give a wider area of irritation. In view of this, it is best to treat only one area at a time, e.g. the forehead for four weeks, before moving on to another area.

It can be applied less frequently if the licensed dosing is not tolerated. In pulsed dosing it is applied twice daily for one day each week until lesions are cleared, or for a maximum of nine weeks.
Daily application for six weeks has also been employed. It works best on the face. It eliminates sun-damaged cells, giving an anti-ageing, smoothing effect to the skin.

AC responds to 5FU, but inflammatory response on the lips tends to be even more pronounced. Potent topical steroids may be needed to control inflammation.

Diclofenac gel
This is available as a 3% gel in hyaluronic acid. Diclofenac’s therapeutic effect is thought to be mediated through inhibition of the cyclo-oxygenase and arachidonic pathway. It is applied twice daily for 12 weeks. It should be applied to all the treated area. Areas measuring up to 50-80cm² can be safely treated. The gel is well tolerated, giving rise to minor irritation in some patients. The numbers of AKs are reduced by 70%. The therapeutic response may only be evident in the month following treatment cessation. It is an option for areas of extensive AKs when destructive therapies or irritation are not desirable.

Imiquimod
Imiquimod is an immune-response modifier that activates host immunity against tumour cells. It is licensed for AKs on the face and scalp in immunocompetent patients. It is applied three times per week for 16 weeks. It is available as a 5% formulation for lesion-targeted treatment. It has a 95% response rate.

Inflammation and crusting are common and ulceration may result. A severe inflammatory reaction is associated with a better therapeutic response. The frequency of application may have to be reduced if inflammation is excessive. A systemic effect may lead to flu-like symptoms. As with 5FU, it is best to treat only one area at a time, in view of the brisk inflammatory response.

Bowen’s disease
BD presents as a slow-growing, well demarcated, erythematous plaque. It is often misdiagnosed as a patch of eczema or a plaque of psoriasis. An isolated, scaly lesion not responding to topical steroids should be biopsied to exclude BD. The edge tends to be irregular and the surface slightly palpable and moderately thick AK. It is applied as outlined previously. A new 3.75% formulation containing 0.5% FU in combination with salicylic acid (a keratolytic) will soon be available. It is licensed for field-directed therapy. It is approved by the FDA for two weeks of daily treatment, two weeks of non-treatment, followed by a final two weeks of daily treatment.

New and upcoming treatments
Ingenol mebutate gel
This is a field-directed topical therapy recently approved by the FDA. There are two different concentrations of the gel. For treatment of the face and scalp, 0.015% gel is applied once daily for three consecutive days. For the body, 0.05% is applied once daily for two consecutive days. It works by directly killing dysplastic cells and by inducing an immune response. The main side-effect is a mild to moderate inflammatory response at the site of application. The short course of treatment required with ingenol mebutate is an advantage. It is anticipated it will be available in Ireland next year.

New concentration of imiquimod
Imiquimod 5% is available for lesion-directed treatment as outlined previously. A new 3.75% formulation will be available for field-directed therapy. It is approved by the FDA for two weeks of daily treatment, two weeks of non-treatment, followed by a final two weeks of daily treatment.

New formulation of 5FU
A 5% formulation of 5FU is already available. A new formulation containing 0.5% FU in combination with salicylic acid (a keratolytic) will soon be available. It is licensed for slightly palpable and moderately thick AK. It is applied daily using an integrated brush. Irritation is common and has been reported as severe in 28% of treated patients. Frequency of application should be reduced if severe irritation develops. Evidence suggests it may be better than cryotherapy for lesion-directed therapy, with a lower recurrence rate.

Conclusion
We are going to see more and more AK in primary care. The vast majority of patients presenting should be adequately managed in primary care and constant updating of skills using new therapeutic options are required.

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