Actinic keratosis (AK) is a common sun-induced precancerous neoplasm confined to the epidermis. In the years between 1990 and 1994, patients had almost 3 million annual visits to dermatologists for AKs [1]. The AK is the initial manifestation of a continuum of clinical and histologic abnormalities that progresses to invasive squamous cell carcinoma (SCC) [1–35]. A review of 459 cutaneous SCCs showed that 97% were associated with a contiguous AK [28]. The major risk factors for the development of AKs are accumulated solar exposure and intense, recent exposure.

Bowen’s disease, also known as squamous cell carcinoma in situ, represents early SCC confined to the epidermis. The continuum of dysplasia, in situ carcinoma, and invasive SCC in the skin is analogous to the well-accepted changes seen in dysplasia of the uterine cervix. Early malignant changes on the skin can be detected during incipient stages of evolution and thus be treated in the premalignant and preinvasive stage.

SCC of the skin accounts for thousands of preventable deaths in America each year. More than half of all SCCs contain p53 tumor suppressor gene mutations; such p53 gene alterations are also common in the AK and may work synergistically with ultraviolet light to account for its malignant character. Like SCCs, the vast majority of AKs and Bowen’s disease lesions are asymptomatic. Although some lesions may become clinically inapparent because of immune rejection or simply because their external surfaces have been unknowingly scraped off, an untreated AK represents the first sign of a potentially curable fatal cancer.

Each AK and suspicious lesion should be treated before it progresses to invasive SCC. Destructive modalities, such as cryosurgery using liquid nitrogen and electrodesiccation and curettage, usually performed by a dermatologist, are the mainstays of therapy. Each case must be individualized.

**Actinic keratosis**

**Definition**

AK are the most common precancerous skin lesions among light-complexed individuals [1–35]. The lesions are also known as solar keratoses or, less commonly, as senile keratoses. The latter is a less desirable term, because the development of AK is related to cumulative and acute solar exposure, not to increasing age per se. An AK of the lip is known as actinic cheilitis. This condition most commonly affects the lower lip.

**History**

AK has been known by a variety of names, including solar keratosis, senile keratosis, senile hyperkeratosis, keratoma senile, and keratosis senilis [4,5,12,14–25,28–31]. Many prominent clinicians described AK and the changes associated with chronic sun exposure as early as 1894. Clinicians noted the effects of chronic solar exposure on the skin of sailors, farmers, and patients with conditions...
such as xeroderma pigmentosum. Changes in the skin were described as "hyperemia, hyperpigmentation, telangiectasia, atrophy, keratosis or cancerosis; or all, at times in a determined order of succession" [13]. In 1926 [18], the histologic features of AK were described in detail. Hookey in 1931 insightfully reviewed the topic, observing that AKs usually evolve into a SCC or, much less frequently, into a basal cell carcinoma [20].

**Incidence and prevalence**

Numerous studies have been attempted to estimate the true prevalence of AKs in the general population. Inherent biases in the selection of subject populations have led to many different reported prevalence rates [36]. The validity of some studies is questionable [37–39] because inexperienced observers performed the cutaneous examinations. In addition, these studies differ significantly in age distribution, racial mixture, methods of selection, and anatomic sites examined. Most importantly, histologic evaluation has not been performed in any of the studies to date [25].

Many epidemiologic studies analyze the connection between AKs and non–melanoma skin cancer, such as SCC and basal cell carcinoma [36–41]. They link the development of AKs to ultraviolet light exposure. Accumulated, lifetime sun exposure and recent, intense exposure both play a role in the development of AK [1]. The lifetime risk of having SCC after developing a single AK has been estimated at between 6% and 10% [6].

Studies show that the rate of progression to invasive SCC varies from less than 1% of all lesions to 20% of all AKs [7]. Studies have proved that approximately 25% of all AKs remit spontaneously.

**Risk factors**

**Age**

The AK increases in prevalence with advancing age [40–42]. In the third decade of life, a prevalence of less than 10% has been reported, rising to over 80% in pale-complexioned people aged 60 to 69 years [41]. The appearance of AKs in children may be seen in disorders that disrupt normal protective mechanisms against solar damage, such as albinism and xeroderma pigmentosum [2,13,20].

**Gender**

Men are more often affected than women, a difference that presumably reflects more solar exposure in men [41]. One survey indicated a rate of 26.5 per 100 in men, as compared with 10.2 per 100 in women [39]. An Australian study showed that a solitary AK was evident in 63.4% of men and 47.8% of women [32]. A more marked difference may be evident in younger age groups, with 13% of women and 27% of men aged 16 to 49 years affected, as compared with a 56% to 66% difference in people aged 50 to 86 years [40]. Similar results have been shown in other studies [41,42].

**Latitude**

Although the strong correlation between latitude gradients and the prevalence of non–melanoma skin cancer has been shown [43,44], studies linking an increased prevalence of solar keratoses and latitude are less conclusive [25]. Many studies, however, are consistent with the inverse relationship between prevalence and latitude. One study compared Australian-born people with British immigrants in Australia [45]. It found that native-born Australians had a higher prevalence of AKs.

**Anatomic distribution**

The distribution of both AKs and SCC correlates with the most intense ultraviolet light exposure [46–49]. More than 80% of AKs are found on the head and neck, forearms, and other areas with chronic solar exposure [37,38]. The distribution differs by sex, reflecting various hairstyles and other customs that affect ultraviolet exposure. In men, 67% of AKs are on upper limbs and 28% are on the hand, face, or neck, whereas in women the distributions are 63% and 34%, respectively. Subsites differ as well, especially on the face.

**Genetic factors**

Genetic factors that represent constitutional sensitivity to sunlight play a significant role in the development of solar keratoses [8]. Blue eyes, red hair, and childhood freckling are linked to increased risk [8,25]. Mucocutaneous albinism and possibly Rothmund-Thomson syndrome [13,25,50–54] are also linked to AKs. Albinos in northern Tanzania had AKs in childhood, with the youngest being 8 years of age [51]. Albinos aged more than 20 years had a 91% incidence. Another Tanzanian study observed four clinical stages in albinos: erythema, epidermal atrophy with dermal hypertrophy, solar keratoses, and clinical carcinoma, with the solar keratoses occurring only in cutaneous areas after the stages of erythema and epidermal atrophy [50]. Xeroderma pigmentosum is also associated with the development of AK early in life [53,54]. AKs were observed in 19% of patients, but this figure is
probably an underestimate, because the median age at onset of skin cancer was 8 years [54].

Other factors
In addition to the risk factors already discussed, patients with AKs at thermal injuries and large scars have an increased risk of malignant transformation, as do patients with immunosuppressive states (eg, AIDS, organ transplants) and human papillomavirus infections. Increases in ultraviolet radiation exposure due to increased longevity and ozone depletion may account, at least in part, for the increased risk for skin cancer [2,3].

Pathogenesis
The effects of oncogenes, ultraviolet light, and other factors on the induction and progression of AK have been studied [55–74]. The p53 tumor suppressor gene, located on chromosome 17p, encodes for a nuclear phosphoprotein whose functions include allowing for DNA protection, cellular proofreading, and DNA repair [9,71]. Mutations of the p53 gene are now recognized as the most common genetic alteration in AK, in situ SCC, and SCC [9]. Aberrations of the p53 gene are common in AKs. In one study, 69% of cutaneous SCCs and 53% of AKs were positive for p53 mutations [57]. Mutations of p53 may portend progression of an AK into an SCC. Additional fundamental chromosomal alterations in AKs include expression of the homeobox gene HOX-C4 [65] and the presence of activated ras genes [58].

Clinical manifestations
AKs are skin-colored to reddish brown or yellowish black, ill-defined, round or irregularly shaped macules or papules with a dry, firmly adherent scale. The AK is often better appreciated by palpation than by visualization. The lesion most commonly has a rough, scaly texture that resembles fine sandpaper [2,3,75–83]. The AK is usually from 1 to 3 mm in diameter but can reach several centimeters. On occasion, an AK may be proliferative, enlarging up to 4 cm in diameter and recurring despite standard therapy [80–83]. It is usually seen on sun-exposed body regions in persons with many years of prior solar exposure. AKs may be solitary or multiple. Use of sunbeds, including standard light-boxes used in the medical therapy of certain cutaneous disorders, may produce dense, almost confluent clusters of AKs.

The common AK may be divided into five clinical types: erythematous (desquamative-keratotic), keratotic papular, verrucous or papillomatous, pigmented, and cutaneous horn [75,76]. Three unusual variants are spreading pigmented AK, lichen planus-like AK, and proliferative AK [70–73,75–88]. The cutaneous horn type displays marked visible hyperkeratosis, leading to a hornlike mass [89–103]. Other generalized evidence of solar damage may be evident, such as solar elastosis (yellowish coloration of the skin) and cutaneous furrowing. An individual AK is usually asymptomatic; on occasion, it may be associated with mild local irritation and pruritus.

AK occurring on a mucosal surfaces is known as actinic cheilitis. This lesion occurs most notably on the lower lip and may involve a diffuse slight scaling of the entire lower lip [104–120]. Focal hyperkeratosis and leukoplakia may be seen. The vermilion border of the lip loses its usual plasticity, and small wrinkles appear perpendicular to the long axis of the lip. A blotchy and atrophic morphology may be evident, with an indistinct and irregular vermilion border. The risk for invasive SCC is much greater for AKs on mucosal surfaces [3]. Invasive SCC may occur with or without ulceration.

AKs may also develop on the conjunctivae [114–117]. These wedge-shaped, opaque thickenings near the limbus may extend onto the cornea from the scleral conjunctiva. They are usually classified as pinguecula or pterygium.

Histopathology
The AK is the clinical manifestation of cutaneous dysplasia of epidermal keratinocytes. Common signs of cellular dysplasia, including alterations of cellular polarity and nuclear atypia, are all characteristic [2,3,20,121–127]. The dysplasia of AK, by definition, does not extend beyond the basal layer of the epidermis and does not involve adnexal structures. The dysplasia may occur by itself or in association with a concurrent SCC or, rarely, a basal cell carcinoma [2,20].

Epidermal keratinocytes are often more or less basophilic than surrounding keratinocytes. Size and shape are also altered. Some nuclei are enlarged and contain prominent nucleoli. Other keratinocytes may be multinucleated or vacuolated, at times demonstrating mitotic figures. Individual cell keratinization (dyskeratosis) may be seen.

The epidermis is usually hyperkeratotic, with the stratum corneum either loose or compact. Hyperkeratosis and parakeratosis alternate, with the normal hyperkeratosis appearing above an unaffected sweat duct or hair follicle. This alternating hyperkeratosis and parakeratosis is sometimes referred to as the “flag sign” [11]. The granular layer may be thin;
Acanthosis is often irregular. Nuclei in the basal layer may be clustered, with atypical keratinocytes forming small or large downward buds or pseudoduct-like structures from the basal layer. These altered keratinocytes may less commonly go down the eccrine duct and hair follicle. Glands and follicles remain unaltered unless the AK advances so that dyskeratotic cells block the orifices.

The Bowenoid AK resembles Bowen’s disease, both being SCC in situ, except that the keratinocytes show some terminal differentiation at the level of the stratum granulosum. Evaluation of multiple histologic sections through the tissue block of a suspicious AK may be necessary to rule out dermal invasion, representing invasive squamous carcinoma.

The dermis usually displays basophilic degeneration, a mild inflammatory infiltrate of lymphocytes, histiocytes, and variable numbers of plasma cells, and edema of the upper dermis. However, patients with xeroderma pigmentosum often lack these changes.

**Diagnosis and differential diagnosis**

The diagnosis of AK requires skill and experience. The physician can distinguish AK from discoid lupus erythematosus by the absence of atrophy and dilated hair follicles. Seborrheic keratoses generally appear as waxy, stuck-on, tan or brown lesions. Many other disorders must be considered, including benign inflammatory disorders, deep fungal infection, solar elastosis, and other cutaneous neoplasms, such as disseminated superficial actinic porokeratosis, psoralen-induced keratoses, stucco keratoses, and large cell acanthoma [128–139]. On the lower lip, one should also consider necrotizing sialometaplasia, plasma cell cheilitis, granulomatosis cheilitis, faciotal cheilitis, contact cheilitis, and other types of cheilitis. AKs in children or young adults should mandate consideration of albinism or xeroderma pigmentosum [140].

**Prevention**

The ideal approach to preventing the development of AKs is avoidance of excessive sun exposure [141–152]. The use of sunscreens should be advised [140,153]. A prospective randomized trial in 588 people aged 40 years or older in Australia using a sunscreen with a sun-protection factor of 17 concluded that regular use of sunscreen prevents AK development [140]. Special efforts also should be made to protect and educate persons at high risk, including albinos, people with xeroderma pigmentosum [154], blue-eyed, red-headed frecklers, and renal transplant recipients [155]. Because even small increases in solar exposure in susceptible people may lead to an increase in AKs and SCCs, people should be warned of potential sun exposure hazards [144]. Reducing sunlight exposure in childhood may substantially decrease the incidence of AKs and SCCs in later life [45]. A healthy diet may also be of value; a low-fat diet was found to reduce the incidence of AKs [156]. Retinoids may prevent or diminish the formation of AKs in renal transplant recipients [64].

**Course and prognosis**

Determining whether an invasive SCC has developed can be challenging, both clinically and histologically. This difficulty is not surprising given that there is no fundamental difference between an AK and an SCC, but rather progression along a spectrum [68]. The AK may progress to replacement of the entire epidermis by atypical keratinocytes that continue to show differentiation toward the interface with the stratum corneum; the full-thickness dysplasia is designated a Bowenoid AK (SCC, grade 1), an in situ SCC.

The chance of any given AK becoming an SCC is unknown [16,28,149–152,157,158]. Relative risk depends on factors related to the AK itself (eg, thickness), as well as characteristics of the individual patient (eg, drug therapy, degree of pigmentation, immune status). Graham [159] calculated that AKs evolve into invasive SCC in 12% to 13% of untreated patients. Such estimates have differed, the highest being 20% [22]. Other studies suggest that less than 1% of all lesions evolve into invasive SCC [6]. A more recent study found a 6% annualized rate of development of SCC among 203 AK patients [61]. However, this risk may be substantially higher, especially in immunocompromised patients. One Australian study estimated that 60% of SCCs arose from a previously diagnosed AK and 40% from what had been normal skin 1 year previously, producing an annual transformation rate of 0.075% to 0.096% [150]. Assuming an average rate of 0.0075 per year and an average of 7.7 AKs per patient, the probability of at least one AK transforming within a 10-year period is 10.2% [149]. Thus, a seemingly low yearly transformation rate for single AKs represents a significant lifetime risk of transformation for patients with multiple AKs. AK-derived SCCs often have a lower metastatic potential than those derived from arsenical, chronic radiation, and scar keratoses [26,28,32,151,160]. The potential for metastasis is still medically significant as it is estimated that 3% to 6% of AK-derived SCCs metastasize [27,63].
Histologic evidence of a contiguous AK was found in 8 of 18 patients (44%) with SCC that had metastasized from skin [62]. Increased tumor thickness and depth of invasion were the most consistent histologic features linked with these metastasizing SCCs. It has been suggested that AKs are in a state of continual flux, with some becoming more clinically aggressive after solar exposure and some becoming less apparent. Although these AKs may become clinically apparent, perhaps because of immune rejection [12] or simply because their external surface has been unknowingly scraped off, an untreated AK represents a potentially curable fatal cancer.

SCC on mucosal surfaces, most commonly seen on the lip, has a significant metastatic potential. From a study of patients aged less than 40 years residing predominantly in Texas, it is clear that actinically derived SCC of the lip has impressive metastatic change, with at least 12 of 56 patients (21%) succumbing [112]. AK with evolution into SCC may also appear on the bulbar conjunctivae [114–117].

Organ transplant recipients and others who are immunocompromised may have an increased propensity to develop AKs and SCCs [155,161–167]. AKs tend to appear at a younger age than expected in these patients, with those who have significant sun exposure and fairest skin type (never tan, always burn) being most at risk within this immunosuppressed group. In one study of 98 renal transplant patients after 10 to 23 years of immunosuppressive therapy, most of the 28 AKs were seen on the face and hands [167]. The average time from transplantation to development of AKs and SCCs decreases with increasing age and decreasing latitude. AKs have demonstrated an increased malignant transformation rate in these patients [162,165]. Aggressive spindle cell SCC may have a tendency to develop in renal transplant recipients [167].

**Treatment**

A number of treatment options are available for AKs [2,3,30]. Treatment of AKs is most frequently performed by an experienced dermatologist. Destructive modalities, such as cryosurgery by liquid nitrogen and electrodesiccation and curettage, are the mainstays of therapy.

Immunomodulation by topical agents has become an area of growing interest in recent years [168]. Topical 5-fluorouracil is now widely accepted as an effective therapy for extensive AKs. Topical imiquimod, which treats AKs by modulation of gene expression, has also recently been shown to treat actinic keratoses [169]. These two medications are preferred when a patient has severe or diffuse actinic damage and keratoses. Although there are differences in schedule of application and side effects, both have been shown to treat existing AKs, while significantly reducing the incidence of new lesions [170].

Retinoids, such as tretinoin, have long been used to treat and prevent actinic keratoses [171]. Recent studies indicate that diclofenac, which reduces prostaglandin synthesis and inhibits cyclooxygenase and lipoxygenase, can be used topically in a gel preparation for three months [172].

Each actinic keratosis is considered individually, with the choice of therapy based on the affected individual and the location, size, extent, and clinical and histologic features of the keratosis, as well as on physician and patient experience with any given therapeutic technique. When there is deep follicular involvement, physically destructive methods are usually mandatory.

**Bowen’s disease**

**Definition**

Bowen’s disease is defined as intraepidermal SCC with dysplasia at all levels of the epidermis. Controversy exists as to whether these lesions are precancerous, with the risk of future transformation into SCC, or whether they actually represent early malignant transformation. Bowen’s disease is also known as SCC in situ.

**History**

John T. Bowen of Boston described two patients with SCC in situ of the buttock and of the lower leg, respectively [30], in 1912. He predicted that these lesions had “imminent” malignant potential.

**Incidence and prevalence**

Bowen’s disease affects predominantly older white men. In one study, lesions occurred equally on covered and exposed skin surfaces [173]. Another review of 617 patients with Bowen’s disease found that 80% of patients were over 60 years of age at the time of diagnosis, with three fourths of the disease occurring on sun-exposed surfaces. One fifth of these patients had multiple Bowen’s disease lesions. Lesions correlate directly to the degree of chronic sun damage [174]. Another study showed that Bowen’s disease of the vulva appears in women
from their early 20s to 90s, with a mean age of almost 53 years [175].

Risk factors

Chronic sun exposure is the major risk factor for developing typical Bowen’s disease. Lesions can occur in existing epidermodysplasia verruciformis caused by human papillomavirus (HPV) type 5. Chronic arsenic exposure can also produce lesions in non–sun-exposed sites.

Pathogenesis

As discussed in the AK section, oncogenes and the tumor suppressor gene p53 play a significant role in the development of SCC in situ. Mutations of the p53 gene are recognized as the most common genetic alteration in AK, Bowen’s disease, and SCC [9].

Clinical manifestations

The typical lesion of Bowen’s disease is an erythematous, scaly, crusting patch, papule, or macule with sharply defined borders. The lesions can range in size from millimeters to many centimeters (Fig. 1). Lesions are devoid of hair. About one third of patients have multiple lesions. Pigmented cutaneous Bowen’s disease represents less than 2% of lesions [176,177]. Plaques may be composed of confluent reddish lenticular papules and nodules of variable size, tending to extend gradually with age in an annular or polycyclic pattern. Bowen’s disease in the anogenital region and on the eyelid margin may be verrucous. Removal of the typical hyperkeratotic scale can reveal a dull, moist surface. As the lesion expands, spontaneous scar formation may develop. Nodular infiltration with ulceration and fungation signals an invasive transformation [178].

Bowen’s disease in the nail bed, on the intertriginous body regions, and on mucosal surfaces may appear with different clinical features. Bowen’s disease of the anogenital region and on the eyelid margin may be verrucous. On the nail bed it may present as a periungual scaling or an erosion with crusting and nail discoloration [179]. Lesions in intertriginous areas may look like an acute or chronic dermatitis or dark patches. When they appear on the ring finger, one should consider the possibility of induction by a gold ring contaminated with radioactive radon [176,180].

Lesions may be seen on any part of the body, including the mucous membranes of the vulva, vagina, penis, conjunctiva, larynx, and nose. On mucous membranes, SCC in situ may appear verrucous and polypoid, as an erythroplakic patch, or as a velvety erythematous plaque. The last morphology, seen in erythroplasia of Queyrat, is a distinct clinicopathologic variant [173,181] of SCC of the glans penis.

Histology

Bowen’s disease extends through the whole thickness of the epidermis, including stratum corneum and basal layer, although the basement membrane remains intact. Parakeratotic hyperkeratosis is usual. The keratinocytes show loss of polarity, atypia, and mitoses, producing a “wind-blown” appearance [173]. Often, there is prominent acanthosis with elongation and thickening of the rete ridges. Individual cell keratinization can be seen; actual horn pearls may occasionally be evident. Prominent nucleoli are common. Some lesions of Bowen’s disease have marked hyperkeratosis and papillomatosis, to the extent that the clinical appearance of a cutaneous horn may be produced. Other lesions display hyperkeratosis with epidermal thinning. Such cells may appear arranged in nests, occasionally resembling the histology of Paget’s disease. The upper dermis shows an infiltrate of lymphocytes, histiocytes, and plasma cells. The pilosebaceous units may show tumor cells, perhaps explaining the high recurrence rate in Bowen’s disease after superficial treatment [173]. Eccrine sweat ducts are invaded by tumor cells in about 4% of cases [182].
Differential diagnosis

The differential diagnosis of Bowen’s disease is broad and often includes both inflammatory and neoplastic processes. Annular plaques may resemble dermatitis, psoriasis, or lichen planus. Pigmented ones may prompt consideration of superficially spreading melanoma [176]. Other possibilities include amelanotic melanoma, seborrheic keratosis, superficial basal cell carcinoma, verruca vulgaris, seborrheic dermatitis of the scalp, tinea circinata, metastatic carcinoma, intraepidermal epithelioma, and some benign cutaneous neoplasms, such as glomus tumor [177]. A fine elevated translucent border distinguishes the superficial basal cell carcinoma.

Prevention

See discussion of prevention of AKs.

Course and prognosis

At least 5% of patients with Bowen’s disease develop invasive SCC. Once invasive SCC develops from Bowen’s disease, at least one third show metastases unless adequate therapy is provided [173]. At least 14% show multiple malignant or premalignant neoplasms with Bowen’s disease. Approximately 6 to 7 years after onset of Bowen’s disease, at least 42% develop other cutaneous or mucocutaneous premalignant or malignant lesions.

If Bowen’s disease is a sign of visceral cancers, the relationship exists primarily for Bowen’s disease on non–sun-exposed body regions, possibly as a result of arsenic ingestion producing both cutaneous and internal carcinomas [173,183–186]. Graham et al [173] observed that at least 38% of women with anogenital Bowen’s disease had cancer of the genitourinary tract. Other studies have confirmed the association of vulvar Bowen’s disease with predominantly in situ SCC of the uterine cervix [175]. The relationship of forms of Bowen’s disease other than anogenital to internal malignancy remains controversial; a number of negative studies exist [185]. However, it might be wise to evaluate patients carefully for arsenic exposure if they have Bowen’s disease on non–sun-exposed sites and to consider anogenital Bowen’s disease in women as a possible clue to other genitourinary tract cancers.

Treatment

Treatment of Bowen’s disease should be performed by an experienced dermatologist. Each individual lesion is studied and the best treatment modality is chosen. Options include cryosurgery with liquid nitrogen, aggressive electrodessication and curettage, and excision [187].

Topical medications such as imiquimod are now being used to treat lesions of Bowen’s disease [188]. New trials studying the effects of topical gene modulators, used after physical destruction of lesions, are currently underway. Topical imiquimod is now being used as an adjunctive therapy after cryosurgery or electrodessication of lesions. Imiquimod has also been shown to be efficacious in treating Bowen’s disease on mucosal surfaces, such as the penis (erythroplasia of Queyrat) [189].

Laser abrasion with the carbon dioxide laser, generally used cosmetic facial actinic damage correction, is an effective treatment modality for Bowen’s disease [190]. Photodynamic therapy is another option for widespread Bowen’s disease [191]. Cutaneous dermabrasion is an excellent treatment option for selected patients with extensive AKs or Bowen’s disease [192].

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