ABSTRACT

The growing prevalence of nonmelanoma skin cancer (basal cell carcinoma and squamous cell carcinoma [SCC]) is alarming and represents an increasing global health burden. The earliest, clinically recognizable manifestation of cutaneous SCC is the presence of actinic keratoses (AK), rough lesions most often found on the sun-exposed skin of older individuals. An understanding of the clinical significance of AKs, including their risk for progressing to invasive SCC, and the means to recognize these lesions are critical for timely treatment and avoidance of potentially deadly consequences.


The development of actinic keratosis (AK), also known as solar keratosis or keratinocytic intraepidermal neoplasia, is a key event in the progression from photoaged skin to invasive squamous cell carcinoma (SCC) or skin cancer. Until recently, AK was considered a precancerous condition confined to the epidermis. AK is now recognized as an early stage in the development of skin cancer; clinical, histologic, and molecular data all indicate that AK does not transform, convert, or progress into cutaneous SCC but is instead the earliest clinically recognizable manifestation of this malignancy. As such, AK represents SCC in situ in its earliest stages.

Epidemiology

Prevalence

Skin cancer is the most common form of human cancer; more than 1 million new cases occur annually in the United States. Skin cancer will develop at least once in nearly 50% of all Americans who live to age 65. Nonmelanoma skin cancers (NMSC) (ie, basal cell carcinoma [BCC] and SCC) constitute more than 33% of all cancers in the United States. The incidence of SCC has been increasing 4% to 8% per year since the 1960s, and SCC accounts for between 2000 and 2500 US deaths each year. Many of these deaths may be prevented by treating the earliest manifestation of SCC—AK. The American Academy of Dermatology (AAD) has estimated that 60% of Americans aged 40 years or older, in whom AK is predisposed to develop, have at least 1 AK lesion. In northern hemisphere populations, 11% to 25% of adults have at least 1 AK compared with 40% to 60% of adults in Australia, which is reported to have the highest incidence of AK in the world largely because of its proximity to the equator and its vast population of fair-skinned individuals.

Risk Factors

The risk factors for AK are the same as those for NMSC. The most clinically significant risk factor is high-intensity or cumulative exposure to UV radiation, whether it is from substantial outdoor activity, tanning beds, or longevity. Individuals who work outside or reside closer to the equator are at greater risk. Likewise, advanced age is considered a risk factor because it is correlated with increased total exposure to UV radiation. Other risk factors include having fair skin that does not tan, tans poorly, or freckles (ie, Fitzpatrick
type I or II skin), having red or blonde hair, and having light-colored (ie, blue, green, or hazel) eyes. AK is relatively nonexistent in black skin. Although no sexual predilection exists, men tend to have more sun exposure from outside activities and, therefore, are more prone to AK than women. Exposure to carcinogens, such as ionizing radiation, or chemicals, such as arsenic or coal tar, also increases the risk of skin cancer. Persons with certain rare genetic disorders, including xeroderma pigmentosum (XP), Rothmund-Thompson syndrome, Bloom’s syndrome, Cockayne’s syndrome, and albinism, also are at higher risk. For example, XP, a disorder in which DNA damage from UV light is not repaired, is associated with sun sensitivity, extensive freckling, and a risk of skin cancer that is 2000 times that of the normal population. Individuals with XP may develop AKs in early childhood. Finally, immunocompromised patients, such as those receiving chemotherapy, AIDS patients, and organ transplant recipients, are at higher risk for developing AKs.

**Pathogenesis**

Actinic keratoses develop as a result of UV irradiation. It is thought that UV-B irradiation is the primary carcinogen in the pathogenesis of AK, whereas UV-A is synergistic with UV-B. UV-B irradiation has 3 roles in the development of AKs: it induces DNA damage in epidermal cells, it generates mutations in the p53 gene, and it causes immunosuppression. Under normal conditions, the DNA damage caused by UV exposure (formation of pyrimidine dimers) triggers induction of the p53 gene, which leads to cell cycle arrest, thereby allowing damaged DNA to be repaired. However, if chronic UV exposure has mutated the p53 gene, the cell cycle will not be arrested, and the DNA will remain unrepaired. UV-induced p53 mutations also affect the gene’s other role as a tumor suppressor. When p53 is mutated by UV exposure, cells with damaged DNA are freed from apoptotic control. UV light also induces global immunosuppression that limits the immune system’s ability to manage and destroy mutated, proliferating cells. Thus, UV light damages DNA, stalls DNA repair, and allows for unabated growth and proliferation of damaged, potentially neoplastic cells.

**Risk of Progression to Invasive SCC**

Actinic keratoses observed over a period of time have 3 possible outcomes: spontaneous clearing, persistence, or progression into invasive skin cancer, usually SCC. The percentage of AKs that progress to involve the dermis is unknown, and estimates vary depending on the number of risk factors present. Published calculations of the risk for the progression of an individual AK lesion to invasive SCC range from 0.025% to 16% per year, and the average annual risk of progression is approximately 8%. Clinical parameters associated with higher risk include immunosuppression, previous radiation therapy, previous personal or family history of skin cancer, age, Fitzpatrick skin type, and existing degree of photodamage. Dodson et al calculated that during a 10-year period, a person with approximately 8 AKs has a 10.2% probability that at least 1 lesion will invade the dermis. Others have postulated that the number of AKs that will invade the dermis depends on time, and that, if left untreated long enough, it is possible that most will do so.

The progression of AK to invasive carcinoma is consistent with the multistage model of photocarcinogenesis (Figure 1). The 3 distinct stages in this process are 1) initiation, in which UV light induces permanent mutation(s) in the DNA of keratinocytes, including mutations in the ras proto-oncogenes and p53; 2) promotion, in which long-term exposure to promoters (chemical or...
physical agents that have proinflammatory effects) leads to a gradual clonal expansion of transformed cells into a neoplasm (ie, the AK lesion); and 3) conversion, in which the AK acquires additional genetic alterations and undergoes malignant transformation into SCC.

RECOGNITION AND DIAGNOSIS

CLINICAL APPEARANCE

The most common way in which AK appears is as a red, scaling papule or plaque on a sun-exposed area of the body, such as a bald scalp, face, or back of the hand (Figure 2). The lesions also may appear skin-colored, pink, brown, pigmented, or hyperkeratotic, and because of the increasing use of tanning beds, they are increasingly seen in “unexposed” areas. Patients may have a single lesion or several lesions (Figure 3). In the initial phases, a lesion may come and go, thus it may be invisible on any given day. AK lesions typically measure from 1 to 3 mm in diameter but can be several centimeters in size, are often poorly demarcated, and may be confluent. The surrounding skin may show evidence of sun damage, such as broken blood vessels, yellowish discoloration, and blotchy pigmentation. As they progress, the lesions become more apparent and often develop subtle erythema at the base and whitish scale. Eventually, they progress to scaly, thick lesions.

Early AK lesions may be detected more easily by palpation than by visual examination. They often are described as having the texture of fine sandpaper, or as feeling soft, rough, or gritty. Patients may report that the lesions are sensitive to touch or burn, sting, and/or bleed.

CLINICAL VARIANTS

Clinical variants of AK (Figure 4) include the cutaneous horn, a hypertrophic type of AK that results in a conical, hyperkeratotic protuberance above the skin surface; lichen planus-like keratosis (or lichenoid AK); pigmented AK, which may resemble a scaling lentigo; and actinic cheilitis, which is AK on the lower lips. Additional distinct variants include hyperkeratotic, verrucous, confluent, and atrophic types of AK.

DIAGNOSTIC TOOLS

Usually, a diagnosis of AK can be made clinically on the basis of visual examination and palpation as previously described. However, distinguishing between a thick AK and an early SCC is sometimes impossible, and in these cases a biopsy for histologic evaluation is indicated. A biopsy should be done on lesions with pronounced hyperkeratosis, increased...
erythema, or induration to rule out SCC. A biopsy also should be done on lesions that are large; that bleed, itch, or are ulcerated; or that have other unusual features. In particular, a biopsy is indicated when any treated lesion recurs. Using a shave excision then curettage to obtain the biopsy sample has been purported to have advantages over using a punch biopsy because, if the diagnosis is AK, no further treatment is usually necessary. However, a deeper biopsy done by using a small punch is more likely to yield a sample sufficient to diagnose invasive SCC, which may be missed by a superficial and inconclusive shave. Furthermore, a defect caused by a punch may be repaired with a sutured closure to produce a less visible scar than the permanent indentation that may result from a shave biopsy.

**Histopathologic Features and Variants**

Histologically, AK is characterized by atypical cytology, alterations in cellular polarity, nuclear pleomorphism (Figure 5), disordered maturation, and mitotic figures. A characteristic feature of virtually all lesions is focal parakeratosis, which is a sign of abnormal keratinocyte maturation. AK lesions also are almost always seen with bluish-grey, elastotic material in the dermis, which is known as solar elastosis or actinic degeneration. The histologic appearance of AK cells may be indistinguishable from that of invasive SCCs. The only histologic difference between AK and invasive SCC is that AK is confined to the epidermis, whereas invasive SCC invades into the papillary or reticular dermis.

Histologic variants of AK with different features include hypertrophic (characterized by marked hyperkeratosis and papillomatosis), atrophic (characterized by a thin epidermis with minimal hyperkeratosis and very small or absent epidermal retia), bowenoid (characterized by broadened epidermal retia and atypical keratinocytes with disordered maturation that extend through the entire thickness of the epidermis), acantholytic (characterized by anaplastic cells that have lost their intracellular bridges, which causes them to dissociate and form clefts within the epidermis), pigmented (characterized by an increase in melanin in the basal layer and in the atypical keratinocytes and by minimal parakeratosis), and proliferative.

**Differential Diagnosis**

The differential diagnosis of unpigmented AK includes warts (which can be distinguished by the histologic presence of marked digitation with parakeratosis at the tips of the digitation), seborrheic keratoses (which have greasy, brown crusts, sharply demarcated borders, and a nonerythematous base and may occur in nonexposed areas), and seborrheic dermatitis. Pigmented AK must be differentiated from invasive BCC or SCC (which are typically seen as indurated nodular lesions with eroded or ulcerated surfaces and more rapid growth), Bowen’s disease (which is a larger plaque with a sharp outline), discoid lupus erythe-
matosus (which shows dyspigmentation, dilated follicles, and atrophy), malignant melanoma (which is more likely to be black-gray, flat, and have no surface change or erythema), and seborrheic keratosis.11,16

**PREVENTION**

Actinic keratosis is better prevented than managed. Clinicians should routinely remind patients to avoid sun exposure, wear sun-protective clothing, and use sunscreen. The AAD recommends a comprehensive sun protection program that includes seeking shade whenever possible and avoiding excessive exposure to sunlight, especially during peak hours of sunlight intensity (10 AM–4 PM); using a broad-spectrum sunscreen with a sun protection factor of 15 or higher, applying it 15 to 30 minutes before sun exposure, and reapplying it every 2 hours when outdoors, even on cloudy days; wearing light-colored, tightly-woven, protective clothing, such as long sleeves and pants and a wide-brimmed hat; avoiding sun tanning outside or in a tanning salon; and regularly examining one’s skin and consulting a dermatologist if changes are noticed. Individuals at high risk should be examined by a dermatologist on a regular basis. Prevention of AKs and skin cancer should begin in early childhood. Babies younger than 6 months should be kept out of the sun, and sunscreen should be used if babies must be exposed to the sun.29

**MANAGEMENT AND PROGNOSIS**

Currently, clinicians have no means of distinguishing individual AK lesions that will clear or remain stable from those that will progress to invasive disease.19 The AAD recommends treatment to eliminate AKs because of the risk they pose for invading the dermis as SCC.7 Several approaches to treatment are available and can be classified as either lesion-directed or field-directed. Lesion-directed therapies include surgical and ablative methods intended to treat 1 or a few lesions; examples are cryosurgery, excision, electrodessication, and curettage. Field-directed therapies are intended to treat multiple lesions or an entire area at risk; examples include topical treatments, such as 5-fluorouracil, imiquimod, and diclofenac gel, diffuse cryotherapy, chemical peeling, laser resurfacing and dermabrasion, and photodynamic therapy. Combinations of treatments also may be useful, especially for the long-term management of patients with AK.

With continuing surveillance, aggressive treatment, and sun protection, AK lesions can be managed and their progression to invasive SCC prevented. The prognosis for patients with AK who have few lesions and limited sun exposure is good, whereas a person who is chronically sun-exposed and has diffuse lesions has a more guarded prognosis because of the higher risk of a lesion progressing to invasive SCC.11

**CONCLUSIONS**

Skin cancer is the most common of all human cancers1 and accounts for nearly 50% of all cancers in the United States.7 AK and SCC share the same genetic alterations, histologic features, and molecular parameters1; thus, AKs have malignant features from their inception and represent SCCs in situ in their earliest stages.7 If left untreated, AKs can progress, affect deeper tissue, metastasize, and kill the patient.3 However, if caught and treated in their early stages, AKs, as well as most types of skin cancer, are treatable and usually curable.3
REFERENCES