CLINICAL UPDATE ON ACTINIC KERATOSIS*

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ABSTRACT

Cutaneous squamous cell carcinoma (SCC) accounts for approximately 250,000 cancer cases each year in the United States, but is associated with a low mortality rate if detected and treated early. Actinic keratosis (AK) is an important precursor lesion for invasive SCC. The likelihood of AK is increased by a number of risk factors, but especially by long-term exposure to sunlight. AKs typically present as scaly or flaky lesions that are often easier to feel than see. AKs are usually diagnosed clinically—a skin biopsy is often obtained for lesions that have failed to respond to repeated treatment attempts, or to rule out SCC. Patients should be encouraged to use preventive measures, such as sunscreen or sun-protective clothing, to reduce the risk of AK. It is not possible to determine which AKs are likely to progress to invasive skin cancer, or when such progression is likely to occur, thus it is important to treat all AKs. Treatment options may be classified as either lesion directed or field directed. Lesion-directed therapies (eg, cryosurgery using liquid nitrogen) are generally used to remove small numbers of lesions. Field-directed therapies, which affect a relatively large area of skin surface, are used to treat a large number of AKs and also to prevent the appearance of new AKs within a sun-damaged skin region. Several field-directed therapies are available, including 5-fluorouracil, imiquimod, and topical diclofenac. Photodynamic therapy or destructive therapies (eg, dermabrasion and chemical peels) may also be options for some patients. All of these options are associated with high cure rates and a low probability of progression to invasive skin cancer. (Adv Stud Med. 2008;8(2):30-35)

Skin cancer is the most common of all cancer types diagnosed in the United States. More than 1 million cases of skin cancer are diagnosed each year in the United States, accounting for nearly 50% of all cancer cases. In general, skin cancers may be classified as either melanoma or nonmelanoma skin cancer (NMSC). NMSC alone accounts for approximately 33% of cancer cases in the United States, and includes basal cell carcinoma and cutaneous squamous cell carcinoma (SCC). Cutaneous SCC is distinct from oral SCC or SCC of the head and neck, which are usually treated by radical resection and are generally associated with poor treatment outcomes. In contrast, cutaneous SCC is a very treatable condition with a favorable prognosis if detected early. There are approximately 250,000 cases of cutaneous SCC per year in the United States, and there are approximately 2000 to 2500 annual deaths attributable to cutaneous SCC. Further, it should be noted that the prevalence of cutaneous SCC has increased substantially since the 1960s, which may reflect changing lifestyles and increased voluntary sun exposure.
Actinic keratosis (AK) is an important precursor lesion for cutaneous SCC, and is the first visible manifestation of SCC in the skin. Some experts have suggested that AK is actually an early cancer, although it is more typically described as an early precancerous lesion. AKs develop in skin that is photodamaged, and they may eventually progress to SCC in situ and then subsequently to invasive SCC. AK is a very common skin condition, with an estimated prevalence rate of 11% to 25% of adults in North America. According to the American Academy of Dermatology, approximately 60% of adults in the United States who have high-risk features (eg, fair skin) will develop at least 1 AK during the course of a lifetime. Important risk factors for AK include advanced age, fair skin, and chronic sun exposure. AK is more common among men than women, perhaps as a consequence of greater sun exposure. Other risk factors include exposure to carcinogens (eg, arsenic and coal tar), certain congenital conditions that predispose to skin cancer, and conditions that cause suppression of the immune system. Immunosuppressive regimens to reduce the risk of tissue rejection following organ transplantation are associated with a very high risk of AK and invasive skin cancers. Cutaneous SCC is a significant cause of death following organ transplantation, and is the leading cause of death among these patients in some countries.

Although the pathogenesis of AK is not completely understood, DNA damage caused by chronic exposure to sunlight (especially to ultraviolet [UV]-B radiation) is thought to be central to the development of AK. DNA repair mechanisms normally counteract DNA damage that is caused by UV radiation. However, the accumulation of several DNA mutations may overcome these repair mechanisms. Mutations to the P53 gene, which normally acts to suppress many types of cancer, may be especially important in the pathogenesis of AK. Chronic UV exposure also increases AK by inducing immunosuppression. The incubation time for AK is very long, with lesions often appearing 20 to 40 years after periods of extensive sun exposure. It should be noted that chronic low-intensity sun exposure is sufficient to induce the formation of AKs, and that episodes of sunburn are not necessary.

Individual AK lesions may spontaneously remit, they may persist as AKs for a long period of time, or they may progress to SCC in situ or to invasive SCC. The likelihood that a patient will progress from AK to invasive skin cancer is largely a function of the number of lesions and the amount of time that the lesions have been present. Estimates of the rate of progression of individual AK lesions have varied widely, from as low as 0.025% to as high as 16% per year. It has been estimated that a typical patient with 8 AKs would have a 10% chance of progressing to invasive SCC over a 10-year period. Factors that are associated with an increased risk of progression to invasive SCC are similar to risk factors for the initial development of AK, and include older age, male sex, the presence of multiple AKs, chronic immunosuppression, and the type of AK, with some large, hypertrophic AKs and AKs with aggressive histologic features (eg, proliferative AKs) being considered higher risk.

**Clinical and Histopathologic Features**

Actinic keratoses typically appear as red scaly or flaky lesions, sometimes accompanied by crusting. They may also be skin colored, brown, or pink. Regardless of color, AKs typically have a rough, sandpaper-like texture, and they are often easier to feel than to see. Lesions appear on sun-exposed portions of the skin, including the scalp, the face, the dorsal surfaces of the hands, the chest, and the forearms. They may vary considerably in size, from as small as 1 mm to as large as several centimeters in diameter. The typical appearance of AK lesions is shown in Figure 1.
Although several AKs are clearly visible in this figure, it is likely that palpation would identify additional lesions by the presence of a rough, gritty skin surface. There are several different clinical variants of AK, several of which are shown in Figure 2.7,14 Actinic cheilitis is a manifestation of AK that involves the lip (typically the lower lip, which receives greater sun exposure).

Actinic keratosis is usually diagnosed clinically, on the basis of appearance and palpation of the lesion.2 A shave or punch biopsy is a simple procedure that may be performed if there is concern that the lesion has progressed to SCC. A biopsy is not required for the routine diagnosis of AK. The most common reason for skin biopsy is to evaluate a lesion that has not responded to repeated attempts at treatment. Other reasons to perform a biopsy include large lesion size or a lesion that is much larger than surrounding lesions, ulceration, or bleeding.

Actinic keratosis is defined histologically by the appearance of atypical keratinocytes within the deeper portion of the epidermis. Whereas SCC involves invasion of the dermis, AK is confined to the epidermis.16 It may be reliably diagnosed by a dermatopathologist from tissue samples stained with hematoxylin and eosin stain. Characteristic features on histopathologic examination include atypical keratinocytes with loss of polarity, nuclear pleomorphism, disordered maturation, and increased numbers of mitotic features. Surrounding sun-damaged skin may exhibit solar elastosis of the dermis and superficial parakeratosis.14,17

The differential diagnosis of AK includes warts, seborrheic keratosis, seborrheic dermatitis, SCC in situ (Bowen disease), and invasive SCC.7 Seborrheic keratosis appears as gray, brown, or black lesions with a “stuck-on” appearance and dot-like stippling, usually appearing on the back or chest. Seborrheic dermatitis is a yellow, greasy, scale-like dandruff that affects the face and chest. AK may usually be distinguished from SCC by the size and thickness of the lesion (Figure 3), and by biopsy if necessary. Irritated or inflamed seborrheic keratosis and AK may be difficult to clinically differentiate.
ACTINIC KERATOSIS PREVENTION AND TREATMENT

All patients should be encouraged to use simple preventive measures to reduce the risk of skin cancer. Sunscreen with a skin protection factor of at least 30 should be applied to all sun-exposed portions of the skin 15 to 30 minutes before sun exposure. Sunscreen should be reapplied every 2 hours, after perspiring heavily, or after swimming. Patients should be reminded to use sunscreen even on cloudy days. Sun-protective clothing should include light-colored, tightly woven garments with long sleeves and pant legs, and a hat with a broad brim that shields the face, head, and neck. Exposure to UV radiation may be minimized by limiting outdoor activities during hours of maximum solar intensity (between 10 AM and 4 PM). Tanning salons should be avoided. Self-examination may be performed using a large mirror and a hand-held mirror. A regular self-examination for patients with a history of AKs (eg, once monthly) can help to identify skin changes for further evaluation by a physician. Regular examination by a physician is important for patients who are at high risk of developing AKs.

As noted earlier in this article, AKs are associated with a substantial long-term risk of progression to SCC. These cancers are not only disfiguring, but may become metastatic, at which point they are essentially incurable. It is not possible to predict which AKs will eventually progress to SCC. For this reason, professional societies, such as the American Academy of Dermatology, the American Cancer Society, and the Skin Cancer Foundation, recommend treatment of all AK lesions to prevent the progression to invasive cancer. In general, treatments for AK may be classified as either lesion-directed therapy (usually selected for patients with a small number of lesions) or field-directed therapy (treatment of entire regions of skin containing several AKs in close proximity and surrounded by extensive photo-damage). Methyldopa and azathioprine are options for AK lesions to prevent the progression to invasive SCC. Treatment with cryosurgery, surgical excision, and electrodessication and curettage is indicated. Cryosurgery using liquid nitrogen is the most common method of treating isolated AKs, and is especially useful for lesions that are relatively small in diameter, thin, and well demarcated. Liquid nitrogen may be delivered using a cotton-tip applicator or a spray device. These techniques freeze the lesion, forming an ice ball that gradually separates and exfoliates over the next few days. Most lesions respond approximately 90%.

Evidence-Based Practice Recommendations

I. Practice Recommendation: For the treatment of AK, a principal goal in primary care is to minimize the risk of progression of AK to invasive SCC. Therefore, patient follow-up is important, particularly when treating AK, as lesions may recur or progress to SCC. 5-FU, imiquimod, and diclofenac are options for the topical therapy of AK.


Specific Web Site of Supporting Evidence from Approved Source: http://euroderm.org/content/guidelines_keratoses.htm.

Strength of Evidence: The European Dermatology Forum has recently issued updated management recommendations for AK. The guidelines noted that AK is an ongoing disease that requires regular follow-up and long-term management (consensus opinion; strength of evidence, C). The guidelines note that several topical agents have been shown to be effective for AK clearance, including imiquimod (2 randomized, double-blind, vehicle-controlled clinical trials with a total of 473 patients; strength of recommendation, A), 5-FU (consensus opinion, usual practice; strength of recommendation, C), and diclofenac (3 randomized, double-blind, placebo-controlled clinical trials with a total of 441 patients; strength of recommendation, A).

II. Practice Recommendation: Photodynamic therapy is a process in which a photosensitizing agent is applied to the skin, and illumination of the exposed area with light of the appropriate wavelength transforms the photosensitizing agent to a cytotoxic intracellular product. Photodynamic therapy is effective for the treatment of AKs of the face and scalp.


Strength of Evidence: Evidence-based treatment guidelines regarding the use of photodynamic therapy for nonmelanoma skin cancer were developed by the International Society for Photodynamic Therapy in Dermatology. The authors identified 6 randomized, double-blind, controlled clinical trials (with a total of 673 patients) demonstrating the efficacy of photodynamic therapy for the treatment of AK (strength of recommendation, A). Treatment response rates in these studies were approximately 90%.
completely to a single application of liquid nitrogen when treated with adequate freezing times (5–20 seconds). If liquid nitrogen is not available, light electric cautery followed by curettage is sufficient in most cases. Surgical treatment is sometimes used for AK lesions, and also provides diagnostic information for a suspected SCC.

Field-directed therapy is useful when it would be impractical to freeze all of the lesions individually. In addition, the presence of several lesions within an area of sun-damaged skin suggests the possibility of additional subclinical AKs. Field-directed therapy of the entire area treats both the visible lesions and these subclinical lesions, which might develop over the next several months without treatment. Several topical medications are available for field-directed therapy of AK. Topical 5-fluorouracil (5-FU) has been used for decades to treat AK, and remains widely used for this indication. Imiquimod is a topical immune modulator that locally stimulates antigen presenting cells, resulting in increased release of inflammatory cytokines at the application site. Imiquimod may be less irritating than 5-FU, but may also produce a somewhat lower rate of complete AK removal. Diclofenac, which is available in a topical gel, is a nonsteroidal anti-inflammatory drug that significantly reduces AK lesions, but is generally considered less efficacious than imiquimod or 5-FU. All of these agents are typically applied for several weeks (typically, 8–12 weeks or even up to 16 weeks in some cases). The goal of treatment is to produce a vigorous inflammatory reaction, resulting in redness, crusting, and swelling. In clinical studies of field-directed therapy for AK, the magnitude of this response has been significantly associated with the eventual response to treatment. This response must be maintained at an intensity that is just short of unbearable for the entire duration of treatment. The use of these agents in clinical practice is described in more detail in a patient case study presented later in this monograph by Neil Brooks, MD.

Photodynamic therapy is another option that is effective for the treatment of widespread AKs. The lesion is treated with a photosensitizing agent (5-aminolevulinic acid) that is taken up preferentially by dysplastic cells or altered cells. Upon exposure to an appropriate light source, the photosensitizing agent is converted to a cytotoxic chemical. Photodynamic therapy usually produces complete clearing of AKs with a single treatment session. Adverse effects include acute stinging or burning, which resolves within 24 hours, in addition to redness and scaling that may persist for approximately 1 week. This approach is often useful for individuals who have employment or social responsibilities that require frequent public interaction or who otherwise prefer to avoid the chronic daily treatments required with the topical agents described previously.

Destructive therapies, such as dermabrasion or chemical peels, are not used specifically for the treatment of AK, but may be used after treatment for cosmetic reasons. Laser resurfacing using a carbon dioxide laser has also been used for this purpose, although anecdotal reports have suggested that laser resurfacing may actually increase the risk of AKs in susceptible individuals (Jeffrey Dover, personal communication).

**CONCLUSIONS**

Actinic keratosis is a common condition that may progress to invasive SCC if not treated. It is not possible to predict with certainty which AKs will progress to SCC, thus treatment of all AK lesions is recommended by several professional societies. AKs are easily identified by appearance and palpation, and generally respond well to a range of treatment options. Nearly all of the deaths caused by invasive SCC in the United States are preventable by the early recognition and treatment of AKs.

**REFERENCES**


