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ACTINIC KERATOSIS: IDENTIFICATION AND TREATMENT

Lesion- and field-directed therapies thwart precancerous lesions before skin cancer forms. By Gary Goldenberg, MD

NON-MELANOMA SKIN CANCERS (NMSC) are the most common cancers in humans. In fact, an estimated 2 million NMSC were diagnosed in 2004.[1] One quarter of those individuals had the diagnosis of squamous cell carcinoma. Actinic keratosis (AK), the most common neoplasm treated in humans, is a precursor lesion to squamous cell carcinoma, which affects one quarter of those diagnosed with NMSC.

Actinic keratosis is the second most common diagnosis made by dermatologists in the United States. In fact, AKs account for 5.2 million annual doctors' visits per year, with 60 percent of these in the Medicare population.[2] A total of $920 million is spent on the treatment of AK annually; with six percent being spent on topical therapy, 43 percent on office visits, and 51 percent on destructive procedures.

The risk factors for developing AK are similar to that of NMSC. The majority of AKs are on sun-damaged skin, with head and neck, upper and lower extremities being the most common locations. A patient with these risk factors generally has an average of 7.7 AKs. These people are also 10 percent more likely to develop SCC over the course of 10 years.[3] Other literature cites higher estimates at 13 percent to 20 percent over a 10-year period, especially if patients don't seek treatment. Although most authorities consider AKs to be "premalignant," some authors advocate use of the term "keratinocytic intraepidermal neoplasia (KIN)" and consider AK an early stage of SCC, similar to the "cervical intraepithelial neoplasia" classification.[4]

Pathogenesis

Long-term, persistent UV exposure appears to be most important in the development of AK/SCC. The initiating event is usually direct damage to cellular deoxyribonucleic acid (DNA) by UV radiation type B (UVB); this damage in turn may lead to a mutation. If a gene that controls

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cell division is damaged, the result can be uncontrolled cellular growth.[5]

Ultraviolet radiation type A (UVA) is also said to play an important role in tumor promotion. It does so by several mechanisms, including oxidative stress, generation of reactive oxygen species (ROS) and direct cytotoxicity. Signature UV mutations, G:C-to-T:A, are usually found in NMSC and can inhibit DNA repair.[6] UV radiation, especially UVB, is also thought to be responsible for tumor progression. Loss of function of p53, a tumor supressor gene that becomes mutated due to UV light, is also important in tumor progression.[7]

Immunosuppression plays an important role in pathogenesis of AK, and UV radiation can also suppress immune mechanisms in the skin, which is known to play an important role in AK pathogenesis.

Other risk factors include tanning bed use, ionizing radiation exposure, therapeutic radiation exposure, chemical exposure such as arsenic, coal tar and nitrogen mustard, and human papillomavirus infection.[8-10]

Clinical Presentation

AK most commonly presents on sun-damaged and sun-exposed skin, including ears, upper forehead, nasal bridge, temples, malar eminences, dorsal hands, extensor forearms, and the scalp in balding individuals.

Skin traditionally not exposed to the sun, such as mid-lower back and buttocks, may also be involved, especially in patients who frequent tanning parlors. AKs—most common in late middle-aged to elderly patients with light-colored skin—often present as skin-colored to reddish papules or patches with scale.

At times, these lesions are more easily palpated than seen and feel like sandpaper. The size of the lesions varies between several millimeters to over one centimeter. In areas of high UV exposure, AKs may form confluent plaques that may be confused for a rash. Patients may complain of lesion tenderness, regression and recurrence, appearance in crops, and spontaneous bleeding. Spontaneous bleeding is the alert the lesion may have developed into an invasive carcinoma, requiring an immediate biopsy.

Histologically, AK presents with parakeratosis of the stratum corneum, atypical, and enlarged, hyperchromatic keratinocytes along the basal layer of the epidermis. You will also notice signs of sun damage in the dermis, such as solar elastosis and telangiectasia.[11] The keratinocytes along the basal layer show disorganized arrangement and lack maturation with ascent. You may also see mitosis.

Patients can present with multiple clinical types of AK.

Hypertrophic AK (HAK) is usually larger in size and appears as a hyperkeratotic papule or plaque on erythematous base. These lesions may be irritating to the patient, as they may catch on clothes, etc. You can usually note marked hyperkeratosis and epidermal hyperplasia. At times, HAKs develop a cutaneous horn, a thick column of stratum corneum. Although the majority of cutaneous horns are AKs or benign lesions, 15 percent represent SCC, making it prudent to perform a biopsy.[12]

Pigmented AK (PAK) is a variant of AK with brownish pigmentation. These lesions may not show the same level of erythema as "usual" AKs. PAKs are most common on sun-exposed skin with severe solar damage. PAK present with increased melanin deposition along the basal later.

Spreading pigmented AK (SPAK) is a common but uncommonly reported and underappreciated variant of AK.[13] SPAKs are located mainly on sun-exposed areas. Generally larger than 1.5 cm, these lesions typically spread laterally over time. The clinical differential diagnosis of PAK includes solar lentigo, seborrheic keratosis, lentigo maligna and lentigo maligna melanoma. If you have any question about clinical diagnosis, take a biopsy.

Lichenoid AK (LAK) is a variant of AK most commonly confused with basal cell carcinoma. These lesions may be present on sun-exposed skin, but are also seen on upper arms, chest, and back.

Actinic cheilitis (AC) represents AK on mucosal surfaces, most commonly the lower lip. AC presents with multiple scaly papules and plaques, which may be on the entire lower lip.[14] A biopsy may be necessary to exclude SCC of the lip.

Atrophic AK shows atrophy of the epidermis with similar features to epithelial atypia.

Treatment Options

Physicians can choose multiple treatment options, which are divided into two broad categories: lesion-directed therapy and field therapy. For patients with multiple AKs, optimal therapy combines lesion-directed and field based treatments since lesion-directed therapies target clinically visible lesions, while field-directed therapy targets clinical and subclinical lesions.[4]

The following examples show lesion-directed approaches:

• **Cryosurgery.** Cryosurgery (LN2) is the most common treatment for AKs. This modality uses liquid nitrogen at temperature of -196.5 degrees Celsius to destroy tumor cells.[15] Tumor destruction is thought to work by direct effect via ice crystal formation. The intracellular and extracellular crystal formation damages the tissue. Vascular stasis is also important for tumor cell destruction. Production of a series of freeze and thaw cycles is most effective.

The efficacy of LN2 for AK varies depending on the study. A recent prospective study by Freeman and colleagues showed efficacy of LN2 depends on freeze duration. In this study, complete response was 39 percent for freeze times of fewer than 5 seconds, 69 percent for freeze times greater than 5 seconds, and 83 percent for freeze times greater than 20 seconds.[16] This efficacy is lower than previously reported.

The most common side effect of LN2 is hypopigmentation, since the freezing can destroy melanocytes, which may be permanent.

• **Curettage and electrodessication (C&D).** C&D, a well-recognized treatment for HAKs, is not commonly used to treat AKs, but it is a well-recognized treatment for HAKs.[17] This modality uses several cycles (usually two to three) of curettage combined with electrodessication to destroy tumor cells directly.

• **Excision.** Surgical excision with margins may be used to treat AKs, but this treatment is not commonly used and is not advocated since it is not necessary for AKs.

Field-directed therapies also provide another option for treatment

• **5-Fluorouracil (5FU).** Topical 5FU to treat AKs was first reported in 1968.[18] It is available in multiple formulations (0.5%, 1%, 2%, 5% cream, solution or porous Microsponge) for application times of 2 weeks to 6 weeks.[19] The clearance rate of approximately 50 percent has been reported with 5FU.[20] The most common adverse effects include erythema (93 percent), burning (75 percent), pain (44 percent), and erosions (44 percent).[21]

• **Diclofenac gel 3%.** Diclofenac gel is approved for application twice daily for 60 days to 90 days to each lesion site, although most practitioners use it as a field therapy.[22] Complete clearance rates of 34 percent to 47 percent of patients at 30 days post treatment is reported with this modality.

• **Photodynamic therapy.** Aminolevulinic acid and photodynamic therapy uses a photosensitizing drug, ALA, which is converted in tumor cells to protoporphyrin IX.[23] The blue light over 1,000 seconds causes a cytotoxic reaction that kills the tumor cells.[23] PDT is currently indicated for spot treatment of mild-to-moderate AKs on the face and/or scalp. However, most practitioners use this modality for field therapy, off-label. Clearance rates depend on duration of contact with ALA. Seventy-three percent of patients achieved complete AK lesion clearance at 12 weeks with 14 to 18 hours of incubation prior to exposure to blue light, with 30 percent of patients requiring a second round of treatment.

• **Imiquimod (IQ).** IQ is currently approved in two formulations: 5% cream and 3.75% cream. IQ 5% is approved for the treatment of AK, superficial BCC and external genital warts. The AK treatment course involves application twice weekly for 16 weeks, and the complete clearance rate is 45 percent after eight weeks of follow up.[24] Local skin reactions are generally less severe than with 5FU, including erythema (97 percent), pain (3 percent), burning (6 percent), and stinging (3 percent).

Recently approved IQ 3.75% (Zyclara) is optimized for a larger surface area, and patients enrolled in clinical trials for IQ 3.75% had a higher number of AKs at baseline. The treatment uses a cycle therapy approach, with daily application for 2 weeks, followed by 2 weeks off, followed again by 2 weeks of daily application. During the rest period, most patients returned to baseline with respect to erythema. Complete clearance rate for IQ 3.75% is reported at 36 percent.[25] Local skin reactions were milder than with 5FU, and only 10 percent of patients required a rest period during the trials.

AK is one of dermatologists' most common diagnoses and one of the most common neoplasms in humans. Multiple treatment modalities are available and a combination of destructive and field therapy should be used to treat patients with multiple AKs. ■

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