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Actinic keratosis: a new approach to the treatment

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Abstract

Actinic keratosis is an intraepidermal proliferation of transformed, atypical keratinocytes, induced by exposure to solar ultraviolet radiation. Many authors believe that it is the earliest form of squamous cell carcinoma. More than 40% of all metastatic squamous cell carcinomas develop from actinic keratosis. The clinical, histological and molecular characteristics of actinic keratosis are those of squamous cell carcinomas. Since it can be extremely hard to distinguish actinic keratosis from some squamous cell carcinomas, treatment can be rather difficult. The best treatment of actinic keratosis is its prevention. The main reason for therapy which is universally accepted, is prevention of squamous cell carcinoma. A number of options are available, but when considering the efficacy, invasive procedures remain the standard treatment. Treatment of individual lesions may prevent further progression of actinic damage present in the surrounding skin.

Actinic keratosis (AK) is an intraepidermal proliferation of transformed, atypical keratinocytes induced by exposure to ultraviolet (UV) solar radiation. The most common synonyms are "solar keratosis" and "senile keratosis". In regard to the precision of the term: "solar" may be more preferable, but the lesions can be produced by all types of radiation, including radioactive, x-rays, and sun (1).

Current concepts

Many authors share different opinions about the real nature of AK. Some of them think that AK is a "premalignant", or "precancerous" disease, because the lesions are confined to the epidermis, without a metastatic involvement. Other authors believe that actinic keratosis is a squamous cell carcinoma, or squamous cell carcinoma in progress, or incipient intraepidermal squamous cell carcinoma (2-4). "*AKs are malignant in the same sense as Bowen's disease (squamous cell carcinoma in situ), intraepithelial Merkel cell carcinoma, intraepithelial sebaceous carcinoma, intraepithelial melanoma (melanoma in situ), extramammary Paget's disease, and cervical intraepithelial neoplasms (CIN)*" (4).

Epidemiology

After acne vulgaris and nonspecific dermatitis, AK is the third most common reason for visiting a dermatologist. The prevalence rates vary substantially in different geographic areas, from 11 to 40% (5,6). The development of AKs depends on many variables, such as: age, sex, race, place of birth, ethnic origin, place of living, occupation, socio-economic status, and skin type. In the third decade of life a prevalence of less than 10% has been reported, increasing to over 80% in light-complexioned individuals aged 60-69 years (6). Men are more susceptible to develop AKs than women, mostly because they get more sun exposure.

Cumulative, lifetime exposure to UV radiation and, recent intense exposure, are other major risk factors responsible for the development of AK. More

than 80% of all AKs are localized on chronically sun exposed skin, such as the scalp, head, neck, forearms, and on the dorsal aspects of hands. The age at which a person experienced the highest level of exposure to UV radiation, and at which sun burns occurred, is another major risk factor for developing AK. Exposure during childhood is associated with the greatest risk. Thus, Kennedy assessed the effects of painful sunburns and lifetime sun exposure on the risk of AKs and seborrheic warts in relation to the development of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) in 966 individuals. Painful sunburns before the age of 20 years were associated with an increased risk for SCC, BCC and AKs (7).

Etiology and pathogenesis

The aim of some recent studies was to assess the effects of UV light and oncogenes on the induction and progression of AKs (8-10). High frequency loss of heterozygosity on several chromosome arms (17p, 17q, 9p, 9q, 13q) has been commonly found in AK. The most common genetic alteration found in AK and SCC is a mutation in the p53 tumor suppressor gene. Located on chromosome 17p, this gene functions in DNA protection and may account for tumor progression. The frequency of p53 mutation in patients with AK has been estimated to be about 75-80%. The progression of AK into a SCC of the skin, also correlates with deletion of 9p21 region which encodes a p16INK4a tumor suppressor (11). The development of SCC and BCC is the result of a complex sequence of events, initiated by exposure to UV light. The initial damage takes place in the DNA, and most of the UV-induced lesions in the DNA are repaired (23). The progression from stimulus to neoplastic transformation and to metastasis is presented in Fig. 1. (4). Tenascin (extracellular matrix protein) expression in AKs is related to the stage of dysplasia and plays a role in neoplastic progression working as an anti-adhesive factor (13).

Thomas and associates believe that keratinocytes in hypertrophic AK live longer and probably have higher propensity for additional mutations and conversion to overt SCC (14).

Histopathology

Microscopic changes are confined to foci in the epidermis with atypical aggregates and pleomorphic keratinocytes at the basal cell layer, which may extend to the granular and cornified layers. The epidermis demonstrates an abnormal architecture because of irregular acanthosis. In the basal cell layer, nuclei may be clustered with atypical keratinocytes forming buds or pseudo ducts in the papillary dermis. The

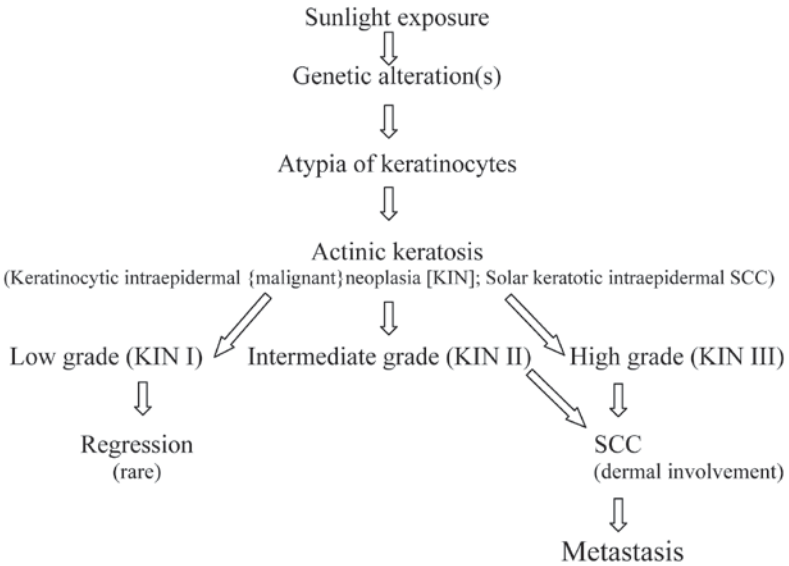

Figure 1. Postulated steps in the pathogenesis of squamous cell carcinoma (SCC) induced by ultraviolet rays (4)

basal cell layer appears more basophilic, because of the crowding of atypical keratinocytes. Dyskeratotic, even multinucleated or vacuolated cells may also be found. The adnexal epithelium is spared, with orthokeratosis overlying these structures, giving rise to the characteristic pattern of alternating orthokeratosis (or hyperkeratosis) and parakeratosis („flag sign") (15).

AK is almost always associated with solar elastosis in the dermis, and lack of solar elastosis should cause reconsideration of the diagnosis unless the patient has genodermatosis with abnormal DNA repair (4). Several histological, with corresponding clinical types have been described: pigmented, hypertrophic, atrophic, bowenoid, epidermolytic, lichenoid.

The relationship between AK and Scc

The pleomorphic and atypical keratinocytes are covered with an abnormal, parakeratotic cornified layer that is rough and appears as a crust of a horn-like texture. Though many factors can affect its further course, the crucial role depends on the host immune response. These lesions may either remain stable or enlarge and extend into the dermis. Once neoplastic cells grow into the dermis, they are referred to as SCC (4).

Clinical features

Actinic keratosis has several clinical variations: erythematous, hypertrophic, keratotic papular, verrucous, pigmented, actinic cheilitis, cutaneous horn, acantholytic, solitary lichenoid, proliferative multiple, atrophic, and spreading pigmented.

Cutaneous horn represents a hypertrophic type of AK and 15.7% of these cutaneous horns are SSC (16). There is no way to distinguish cutaneous horn, a type of AK, from SSC without skin biopsy. Pigmented AK can resemble scaling lentigo, which has histological features of AK. Conjunctiual actinic keratosis is termed pinguecula or pterygium.

Definitiely, there is no way to distinguish AK from SCC without performing a biopsy. An increase in thickness, redness, pain, ulceration and size, may suggest a progression to SCC, but these are not absolutely reliable criteria (4).

Treatment

Generally, since there is no way, neither clinical nor histological, to determine which lesion will progress, invade the dermis or even metastasize, every AK has to be treated (17).

There are many treatments that are highly effective for AK (Table 1). Cure rates over 90% are not unusual. When deciding what therapeutic modality should be used, final decision should be based on the following aims: prevention of progression and metastasis; cosmetic results; and symptom relief.

Table 1. Treatment modalities of Actinic keratosis

Modalities	
Cryosurgery	Excisional surgery
Curretage with and without electrosurgery	Oral retinoids
Topical 5-fluorouracil	Interferon
Imiquimod	Photodynamic therapy
Cryosurgical peel	Topical tubercidin
Laser	Solasodine glycosides
Dermabrasion	Calcitriol and isotretinoin
Tretinoin and other topical retinoids	Diclofenac in hyaluronic acid gel
Chemical peel	

Although a number of different options are available, they are not equally effective in all patients. Actinic keratosis has a wide range of clinical presentations and every individual patient is unique (18,19).

The best treatment is prevention, because the primary cause of AK is excessive exposure to UV light rays. Thus, with reduced sunlight exposure in childhood, one can substantially decrease the incidence of AKs and SSCs in later life. Sun protective clothing, sun screens (applied twice daily for 7 months) and avoidance of sunlight, can protect patients from UV light and prevent formation of AK. However, there are several factors affecting which therapy should be chosen, such as: the patient himself, type of lesion, physician's experience with a certain option, and availability of different treatment alternatives.

According to Dienhart, all treatments for AK can be divided, due to their utilization, into common, less common and uncommon (18).

Cryosurgery

In many countries cryosurgery is the most common treatment method of AK and liquid nitrogen is the most widely used cryogen. Basically, it is a invasive method of treatment, which is relatively easy to perform (both single and double freeze-thaw cycles can be used). The cure rate is higher than 95%. Sometimes it is associated with blistering, crusting, hypo- or hyperpigmentation and even scarring of the treated area. Pretreatment with topical 5-fluorouracil may enhance its efficacy and reduce the duration of treatment as well as side effects of both techniques. Extensive cryosurgery, known under the term cryopeeling, can be used for treating fields of AKs.

Curettage

Curettage is another effective treatment of AK. This technique is very suitable for patients with a few lesions, for lesions left after biopsy, as well as for hypertrophic AKs. Curettage may be followed by electrosurgery which will destroy atypical cells and provide hemostasis. Minimal use of cautery enhances the final cosmetic result. Whenever precise histological evaluation is needed, curettage or excisional surgery are of value.

Topical chemotherapy

Topical chemotherapy with 5-fluorouracil is frequently used in the treatment of AK. The efficacy and tolerability of 5% 5-FU cream and 5% imiquimod cream (not licensed for AKs) were compared in one 2007 study, and the authors concluded that 5% of 5-FU remains the gold standard therapy of extensive AKs (20). It blocks the methylation reaction of deoxyuridylic acid to thymidylic acid and thus interferes with DNA and RNA synthesis (21). The standard method consists of 5-FU application to the affected region twice-daily during 2-4 weeks. Pretreatment or concurrent treatment with topical tretinoin of AKs localized on forearms and dorsal aspects of hands represents a more effective method than application of 5% of 5-FU cream alone (15).

Less common treatments of AK include dermabrasion, chemical peels (35% of tri-chloroacetic acid alone, or combined with 70 % glycolic acid) or dermabrasion, cryopeels, laser therapy, photodynamic therapy, salicylic acid ointment and masoprocol cream.

Photodynamic therapy

Photodynamic therapy (PDT) is also an invasive procedure with some specificity for malignant cells. PDT involves application of topical 5-aminolevulinic acid (5-ALA), which accumulates preferentially in dysplastic cells, in combination with light therapy. Exposure to light of appropriate wavelength generates oxygen free radicals, causing cell death. Some studies have shown that if patients with AKs were to choose between methyl aminolevulinate-photodynamic therapy (MAL-PDT) and cryotherapy (which seems to be more superior for thicker lesions), they would significantly prefer MAL-PDT, because it is a more attractive option with comparable efficacy and superior cosmetic outcome (22). Response rates to two cycles of PDT, predominantly on the scalp and face, range from 69% - 91%. The cost-effectiveness is not established. PDT is of value in treating multiple AKs, or those situated on the lower legs or other sites of poor healing (23).

Laser therapy

Resurfacing of the skin, by use of CO2 or erbium laser, removing the skin surface, can remove nonspecifically

dysplastic cells within the epidermis as well. When treating more aggressive lesions which invade the follicular epithelium, scarring and prolonged redness may appear.

Retinoids

Retinoids normalize abnormal keratinization by inducing terminal differentiation or apoptosis in abnormal keratinocytes. Unfortunately, monotherapy with retinoids failed to be successful for AKs. A dose-related response has been reported.

Use of systemic retinoids may be justified in organ transplant recipients, since it has been presumed that these patients are at high risk of progression from AK to SCC (23).

Topical diclofenac

Three percent topical diclofenac in a 2.5% hyaluronic acid gel is a relatively new option in the treatment of AKs. It should be applied on the target lesions twice daily during 60-90 days. According to Karadaglić (Karadaglić Đ, unpublished data), this therapy has limited efficacy. However, in Merk's opinion, 3% diclofenac is a rational choice for early treatment since it minimizes any possibility for progression to SCC (24).

Other therapeutic options include interferon, topical immune response modifiers (IRMs), alpha-hydroxy acids, salicylic acid (2% ointment for its emollient and mild keratolytic effects, either alone or as a pretreatment for topical 5-FU).

Topical immune response modifiers

Topical immune response modifiers (IRMs) alter the skin immune system and stimulate the innate and adaptive mechanisms capable to clear precancerous and even some fully transformed malignant keratinocytes (25). Imiquimod, a 5% cream-based IRM compound, is an immune potentiator with clearly defined immunologic parameters.

Standard protocol in the treatment of AKs includes application of 5% imiquimod cream, twice or three-times weekly, during 4 weeks. After a week-rest-period, the therapy can be repeated completely, if lesions still persist. Complete clearance occurred in 50 % of all patients treated in such way (26).

Retinoic acid, applied 1-2 weeks prior to imiquimod therapy, should enhance the results.

Guidelines

The main reason for treating AKs, which is universally required, is prevention of SCC. Treatment of individual lesions may prevent further progression of actinic damage already present in the surrounding skin (23).

There are several therapeutic guidelines for AKs, but even though new topical treatments still evolve, if we consider the frequency of use, efficacy and benefits against side-effects, as well as cost control, invasive procedures remain the standard of care (27).

It is very important for clinicians to know the indications for biopsy. Bleeding, induration, rapid growth and pain, are highly suggestive of progression to SCC (18). Progression to SCC is more likely if unresponsiveness to standard treatments for AK occurs. Such lesions should be treated as SCC, and not as AKs (18).

There are evidences that at least 40% of all metastatic SCC begin as AK (28). The prevalence of 82.4% of prevalence of concomitant AK and cutaneous SCC in Mittelbronn's and associates biopsy-population, suggest a strong correlation between the two lesions. In 26.7 % of these lesions, SCC arose from AK (29). Variable rates of progression to invasive SCC were reported, the prevalence between 10% - 15% reached the consensus (30). Since there is no way to predict which lesion will progress to SCC, with a 100% accuracy, the treatment of all lesions is strongly recommended. The failure to treat AK may have serious consequences for the patient. In a state of continual flux, even when clinically unapparent after immune rejection or because of scraped surface, if untreated, it may still become an invasive SCC (30). Clinical, histological and molecular features of AK are those of SCC. AK is the earliest manifestation of this malignancy (3). Evans and Cockerell wrote: „Actinic keratosis: time to call a spade a spade" (31).

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Aktinična keratoza: novi pristup lečenju

Savremeni koncept: Aktinična keratoza je neoplazma sastavljena od proliferacije aberantnih keratinocita, ograničena na epiderm. Mnogi autori je smatraju početnim spinocelularnim karcinomom. Više od 40% metastaza spinocelularnog karcinoma počinje kao aktinična keratoza.
Učestalost: Javlja se često, čak 11-25% stanovništva oboleva od nje. Prevashodno su zahvaćene osobe stare 60-69 godina, iako, do 10%, mogu oboleti osobe stare 20-29 godina.
Etiologija i patogeneza: Za nastanak oboljenja značajni su dugotrajno izlaganje suncu, imunosupresija i genetski faktori.
Klinička slika: Znaci i simptomi variraju ne samo po izgledu već i po lokalizaciji (usne, koža, konjuktive, sa ili bez ulceracije itd). Postoji više tipova aktiničnih keratoza.
Patohistologija: Kliničke, histološke i molekularne karakteristike su kao i kod nekih spinocelularnih karcinoma.
Lečenje: Glavni razlog zašto svaku aktiničnu keratozu treba lečeti je prevencija spinocelularnih karcinoma. Pošto ih je nekada teško razlikovati, lečenje može biti otežano. Najuspešnije lečenje aktiničnih keratoza je njihova prevencija. Primenjuju se i brojne metode koje se smatraju uobičajenim (kriohirurgija, kiretaža sa ili bez elektrohirurgije, topijski 5-fluorouracil), manje uobičajene (dermoabrazija, hemijski ili kriohirurški piling, laser, tretinoin, alfa hidroksikiseline) i ređe (ekscizija, oralni retinoidi, fotodinamička terapija, diklofenak).
Zaključak: Destruktivne procedure ostaju standard u terapiji aktiničnih keratoza. Lečenje mora biti efikasno, kako bi se zaustavila njihova progresija. Lečenjem individualne promene, može se zaustaviti progresija aktiničnog oštećenja okolne kože.

