Brief Communication

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Actinic Keratosis

Chieh Chen[1,], Da-Ming Liao[2], Guan-Hong Lin[3]*

Actinic keratosis (AK) is an early skin lesion of squamous cell cancer caused by irradiating ultraviolet rays from the sun and it is also one of the most common skin cancers in humans. Squamous cell carcinoma of the skin is usually present in the basal layer of epidermis as early as adolescence. Therefore, it is necessary to avoid excessive sun exposure at a young age to appropriately prevent AK of the skin, especially for the first-line physicians who practice medicines in rural and fishing villages to discover skin lesions early and provide treatment or refer them to specialist for further therapy. They are able to teach villagers how to prevent the disease and regularly follow up on the progress of skin lesions related to AK.

Key words: actinic keratosis, seborrheic keratosis, ultraviolet radiation, squamous cell carcinoma in situ

Introduction

Actinic keratosis (AK) is a common early precancerous skin lesion in clinical practice which often occurs in the face, ears, scalp, arms and other sun-exposed body parts. As our life span increases, the incidence of skin cancer is more and more, including squamous cell carcinoma and basal cell carcinoma, in which squamous cell carcinoma is the second most common skin cancer after basal cell carcinoma. When the skin become AK, it is clinically about 10% of AK progresses to carcinoma, as the lesions are often mistaken for senile plaques.[1]

Epidemiology of actinic keratosis

AK is the precancerous lesion of squamous cell carcinoma in situ. It occurs more in middle-aged and elderly people, especially often in men, and is associated with prolonged exposure to sun, which is quite common in Western countries.[1,2] It is estimated as the second most common skin cancer in the United States, accounting for more than half of the population over 40 years in age and the incidence rate is the highest in agricultural and fishing villages. According to studies, the likelihood of developing AK will double with every 10 years of age and even rapidly inclines after the age 70.[3] The prevalence rate of AK in Asian population is relatively low (2.27 – 3.75 per 10,000 people/year) when comparing with that in the Western population; for example, in a nationwide cohort study from 2003 to 2011 in Taiwan, and only 0.52% of dermatology patient in China were diagnosed with AK from 2008 to 2012.[4,5]

Clinical features of actinic keratosis

Early diagnosis of AK is not easy; therefore, in recent years, non-invasive dermatoscope is used to examine the skin lesions and

From the [1]Department of Family Medicine, Hualien Armed Forces General Hospital, Hualien; [2]Departments of Dental, Puli Christian Hospital, Nantou; [3]Departments of Family Medicine, Zuoying Armed Forces General Hospital, Kaohsiung, Taiwan.

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* Address reprint request and correspondence to: Chieh Chen, Department of Family Medicine, Hualien Armed Forces General Hospital, No. 163, Jiali Road, Xincheng Township, Hualien County 971051, Taiwan
Tel: +886-928-698-950, E-mail: guppy5230@yahoo.com.tw

has become a practical auxiliary tool of diagnosis, allowing physician to quickly identify the disease. There are specific and diagnostic features that enable confident diagnosis of pigmented and non-pigmented AK and squamous cell carcinoma in situ. The process of skin carcinogenesis is the gradual accumulation of gene mutations of multiple stages, such as caused by exposure to sunlight and involved several different stages: initiation stage, promotion stage, progression stage, and metastasis. Radiation and many chemical carcinogens act by damaging deoxyribonucleic acid (DNA) and inducing mutations. These carcinogens are generally referred to as initiating agents, since the induction of mutations in key target genes is thought to be the initial event leading to cancer development. Some of the initiating agents that contribute to human cancers include solar ultraviolet radiation (the major cause of skin cancer). At the cellular level, the development of cancer is viewed as a multistep process involving mutation and selection for cells with progressively increasing capacity for proliferation, survival, invasion, and metastasis. The first step in the process, tumor initiation, is thought to be the result of a genetic alteration leading to abnormal proliferation of a single cell. Cell proliferation then leads to the outgrowth of a population of clonally derived tumor cells. Tumor progression continues as additional mutations occur within cells of the tumor population. Some of these mutations confer a selective advantage to the cell, such as more rapid growth, and the descendants of a cell bearing such a mutation will consequently become dominant within the tumor population. The process is called clonal selection, since a new clone of tumor cells has evolved on the basis of its increased growth rate or other properties that confer a selective advantage.[1] Clonal selection continues throughout tumor development, so tumors continuously become more rapid-growing and increasingly malignant. The clonal origin of tumors does not, however, imply that the original progenitor cell that gives rise to a tumor has initially acquired all of the characteristics of a cancer cell. On the contrary, the development of cancer is a multistep process in which cells gradually become malignant through a progressive series of alterations. One indication of the multistep development of cancer is that most cancers develop late in life. Such a dramatic increase of cancer incidence with age suggests that most cancers develop as a consequence of multiple abnormalities, which accumulate over periods of many years.[1,6]

Pathogenesis and biological impact of actinic keratosis

Actinic keratoses (AKs) are defined clinically as erythematous, scaly plaques that occur on sun-damaged skin and are a result of exposure to ultraviolet radiation. Excessive exposure to ultraviolet (UV) radiation is the major factor, acting as a complete carcinogen, both inducing and promoting tumor expansion. UV radiation activates molecular signaling cascades that result in modifications of regulatory cytokines levels, immunosuppressive effects, and defective cell differentiation and apoptosis. UV radiation is divided into UVA, UVB; about 94% – 97% of the radiation that reaches Earth's surface is composed of UVA rays, UVB rays are partially absorbed by the ozone layer and represent only 3% – 6%, and UVC rays are filtered by the ozone layer in the atmosphere and only minimum levels reach the earth's surface.[6,7] UVA radiation (320 nm – 400 nm) penetrates the skin more deeply and stimulates reactive oxygen species production, which damage cell membranes, their nuclei, and proteins; in addition, UVA promotes guanine to thymine replacement mutations in DNA. As a result, signal transduction and cellular interaction pathways are affected and abnormal cell proliferation occurs. UVB radiation (290 nm – 320 nm) is absorbed by cellular DNA, promoting errors in the repair of cyclobutane pyrimidine dimers and production of 6 – 4 photoproducts, as well as characteristic cytosine-thymine DNA substitu-

tions. These effects result in mutations in the p53 protein, which regulates the cell cycle and acts on DNA damage repair, mutations in the telomerase gene, and increase of proinflammatory cytokine production. Thus, mechanisms involved in the onset of AKs include inflammation, oxidative stress, immunosuppression, impaired apoptosis, cell cycle deregulation and cell proliferation, and tissue remodeling.[8] They are typically located on the face, scalp, neck and extremities. The most commonly mutated gene in AK is TP53. Other common mutations include ras genes, c-myc protooncogenes, p16INK4a tumor suppressor genes, and associated telomerase activity.[6-8]

Discussion

Actinic keratosis pathogenesis and clinical course

To realize the potential of precision medicine, we need to accelerate the discovery of specific markers of disease and drug pharmacodynamics, as well as metabolite profiles associated with external environment and their associations with disease risk. The clinical significance of AK is that the earliest sign of skin squamous cell carcinoma in situ visible to the naked eye.[3] Approximately 10% of AK will progress to squamous cell carcinoma of the skin, and 60% of squamous cell carcinoma of the skin is originated from its previous state of AK. Its typical clinical features are lichenification and observed with rough, irregular, and ill-defined erythema or rash with some scales and scabs on the surface. Due to the diverse clinical appearance, the patients may also often manifests with seborrheic keratosis, which is looking like senile plaques, as it occurs in elderly patients with prolonged sun exposure. So clinically requiring careful differential diagnosis.[4]

Actinic keratosis treatment

Conventional treatment involves cryotherapy, electrocautery, laser or surgical resection. However, for patient with multiple precancerous skin lesions or lesions of large area and unclear boundaries, which is difficult to treat, or for patient who cannot tolerate the traditional surgical approach, photodynamic therapy can be used.[3-5,7] The lesions of AK are not limited to clinically visible forms but can be seen as widespread precancerous lesions in a specific area, including clinically visible and preclinical ones, and thus, there are two major directions of treatment, which are lesion-oriented therapy and area-oriented therapy.[4]

Lesion-oriented therapy

The options of treatment for clinically visible lesions of AK include cryotherapy, laser and surgery. Cryotherapy is the most commonly used with a clearance rate of 39% to 98.8%. The longer the cryotherapy is, the better the effect on the removal of the lesion, liquid nitrogen cryotherapy is most commonly used. Other methods, including electrocautery, laser or surgical resection are also used.

Area-oriented therapy

The target of the treatment of AK is not only the lesions that are clinically visible to the naked eye, but also the preclinical latent lesions in the area. Currently, there is no standard treatment of AK. The underlying mechanism of a topical photodynamic therapy is to apply photosensitive substance and bombard the cancer cells with light of a specific wavelength to induce a photochemical reaction, resulting in cytotoxicity to kill the cancer cells. Current therapies include some topical skin ointments such as 5-Fluorouracil (5-FU), Imiquimod, Diclofenac, and Ingenol mebutate (methanolic extract of Euphorbia peplus).[3] Advantage and disadvantage of AK treatment (Table 1). The medications have these FDA approve: (1) 5-FU cream: For 2 to 4 weeks. 5-FU is not a treatment option for a woman who is pregnant. This medication can harm an unborn baby. (2) Diclofenac sodium gel: This medication tends to cause less of a

Table 1. Advantage and disadvantage of actinic keratosis treatment.

	Advantage	Disadvantage
Cryotherapy	Cryotherapy is the most common treatment.	Blisters, scarring, changes to skin texture, infection and changes in skin color.
Electrocautery	Electrocautery is a safe and effective method.	Infection, scarring and changes in skin color of the affected area.
Laser	Reduced collateral tissue destruction, decreased bleeding, shorter healing time, and less scarring.	Scarring and discoloration of the affected skin.
Surgical resection	The highest cure rate of all current treatments.	Infection, scarring of the affected area.
Photodynamic therapy	It has no long-term side effects and less invasive than surgery, takes only a short time.	Redness, swelling and a burning sensation during therapy.

skin reaction than 5-FU, but it can still be very effective. You will need to apply it twice a day for 2 to 3 months. While using this medication, you must protect your treated skin from the sun. (3) Imiquimod cream: This can apply it twice a week, so you may need to apply it for 12 to 16 weeks. (4) Tirbanibulin ointment: This may be an option for treating AKs on your face and scalp.

Prevention of actinic keratosis

Asymptomatic AK is often ignored, but as the patient starts to experience pain, itch or tingling sensation with developing red lesions, they are symptoms of inflammatory AK, which are the warning signs to the beginning of progression to skin squamous cell carcinoma.[4] Thus, long-term excessive exposure to UV damage causes microscopic lesions of keratinocytes in the skin, which will eventually turn into skin lesions in old age, commonly seen as AK (precancerous lesions), squamous cell carcinoma, basal cell carcinoma, etc.[3,4,8] A number of smaller studies showed that oral retinoids such as acitretin and isotretinoin significantly reduced the risk of new nonmelanoma skin cancers, although these agents are associated with substantial adverse effects including dry skin, increased lipid levels, hepatotoxic effects, and teratogenicity. Oral nicotinamide was safe and effective in reducing the rates of new nonmelanoma skin cancers and AKs in high-risk patients.

Conclusion

AK is a skin disease caused by sun exposure, generally on areas exposed to sunlight, such as top of the head, the face, and forearms, which may be less prominent as these have rougher surface.[5] The ultraviolet-induced process involves the accumulation of genetic mutations over several stages, including initiation stage, promotion stage, progression stage, and metastasis.[1] The current treatment of the disease includes lesion-oriented treatment for clinically visible lesions and area-oriented treatment for lesions and the surrounding skin, but there is no ideal treatment for the stage of latent lesions.

Author Contributions

Study Design, Chieh Chen and Da-Ming Liao; Data Collection, Chieh Chen; Statistical Analysis, Da-Ming Liao; Data Interpretation, Da-Ming Liao and Guan-Hong Lin; Manuscript Preparation, Chieh Chen; Literature Search, Chieh Chen. All authors have read and agreed to the published version of the manuscript.

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The authors declare no conflict of interest.

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