**Case report and literature review of Actinic keratosis**

Running title: actinic keratosis

**Abstract**

A 94-year-old woman came to the clinic because of itching and pain on the scalp and back, but it was not a typical dermatitis. It is a skin precancerous lesion caused by skin keratinization that may develop into cancer. Primary physicians should be alert to this skin disease. Actinic keratosis 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 young age to appropriately prevent actinic keratosis 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. Primary physicians can educate these villagers how to prevent the disease becoming to skin cancer and are able to teach them how to regularly follow up on the progress of skin lesions related to actinic keratosis.

Keywords: Pre-cancerous squamous cell lesion; Actinic keratosis; Seborrheic keratosis; Ultraviolet radiation; Squamous cell carcinoma in situ.

**Introduction**

Actinic keratosis is an often seen pre-cancerous squamous cell lesion clinically. Actinic keratosis 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. Ultraviolet rays from sunlight are a common environmental cause of skin cancer and it is classified as the first category of carcinogens by the International Agency for Research on Cancer (IARC) (1,2). 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 (2,3). Large-scale studies have shown that the mortality rate of people with sufficient sun exposure at all ages are lower than those who avoid the sun. But sunlight can also cause skin damage, leading to aging and skin cancer (3,4). The typical clinical features include erythematous rash of irregular border with the surface covered by scales and scabs to give it a rough texture to touch (3,5). When the skin become actinic keratosis, it is clinically lead to entered the precancerous stage and will gradually turn into squamous cell carcinoma of the skin if left untreated. Clinically, about 10% of actinic keratosis progresses to carcinoma, as the lesions are often mistaken for senile plaques (5). The increase in the number of skin cancers in the past ten years has placed a heavy burden on medical care in Europe, America and Japan. It is thus expected that aging or cancer resulting from photodamage of the skin will also become a problem for medical care in Taiwan (6-8). Taiwan is located in the subtropical zone, and the intensity of ultraviolet radiation is relatively high. The skin is exposed to ultraviolet radiation anytime and anywhere. Therefore, how to differentiate and diagnose actinic keratosis and senile plaque is even more important. Risk factors for actinic keratosis include skin sunburn from ultraviolet light, human papillomavirus infection, exposure to arsenic-containing substances or arsenic in drinking water, chronic skin inflammation, skin light-sensitive disease, and fairer skin tone ethnic group, etc. This review mainly hopes to introduce and review a case through literatures about actinic keratosis.

**Case Report**

A 94 years old woman, who was suffering from hypertension and osteoporosis (T-score: -3.8), taking medication regularly (Fosamax plus 1# po once weekly). The patient was a housewife in the past and had not been exposed to too much sunlight. With the increase of age, except for a slight increase in blood lipids and osteoporotic lumbar fractures, she has no other diseases. Although the patient does not have multiple systemic chronic diseases, but she had been infected with herpes zoster virus. Therefore, the patient may have lower immunity than normal people. Recently, due to a lichenified skin lesion on the head and back, she seek medical attention because the lesions were itchy and painful. The skin lesions have been found for 2 years, and skin biopsy have been done in other medical centers. Although there are many locations of lesions, there is only one location that is mainly painful. The size of the lesion is about 2x3 cm2. Before she came to the OPD, the lesion was painful, so the patient went to the dermatology department for medical treatment. Although the dermatology department completely removed the lesion, and the pathology report showed no malignant cells, she still felt itchy or painful afterwards, so she came to our hospital for secondary opinion (figure 2). The patient's own liver function and renal function are normal, and the thyroid function is also normal. In the past she had benign fibrous hyperplasia in the right breast which had excised locally with normal CA125 and CA153. Since the patient had visited many dermatology clinics, the urea prescribed by the doctors with steroids or moisturizing had not improved, so her family took her to seek the advice of other family physicians. The skin lesion is as figure 1. Because the patient's skin lesions will be painful; therefore, clinicians suspect the possibility of skin malignancy, so asked the plastic surgeon to do a skin biopsy (histologic images in figure 3). The pathological section report confirmed squamous cell precancerous lesions. The result is that the patients received skin lesion excision and suture, then OPD follow up regularly.

**Discussion**

**Epidemiology of Actinic Keratosis**

Actinic keratosis 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 (1,5,6,7). Although the prevalence rate of this cancer in Asian population is low, it is pathologically more invasive than observed in whites (9). According to studies, the likelihood of developing actinic keratosis will double with every 10 years of age and even rapidly inclines after the age 70 (3,8). The prevalence rate of AK in Asian population is relatively low (2.27-3.75 per 10,000 people per 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 Taiwan were diagnosed with actinic keratosis from 2008 to 2012 (10-13).

**Clinical Features and Diagnosis of Actinic Keratosis**

Early actinic keratosis is asymptomatic and painless, rough, peeling, unevenly pigmented plaques with redness, capillary dilation, and superficial skin ulcerations are common. There are different types of skin lesions in actinic keratosis, and the typical features are keratinization, roughness, abnormal desquamation and scaly plaques on the skin surface, and the location is often exposed to the sun. Actinic Keratosis lesions seen by the naked eye may resemble keratosis or lichenification; but under a dermoscopic examination, it will be found that the epidermis of the lesions is rough and the edges are irregular, and skin flakes will fall off when scratched hard. Due to the diverse clinical appearance, the patients are also often manifests with seborrheic keratosis, which are commonly known as senile plaques, as it occurs in elderly patients with prolonged sun exposure (4,7). Sometimes, the lesion may even show as squamous cell carcinoma of the skin. Skin biopsy is currently the only gold standard of diagnosis (3,14,15,16). However, biopsy, by definition, is still an invasive procedure and given the multiplicity of the lesions, it is impossible to slice every lesion. Invasive squamous cell carcinoma can be difficult to diagnose by dermoscopy alone (12,16). Typical erythematous actinic keratosis, as seen under the dermatoscope, has the characteristic strawberry-red network structure with detail of surface scales and bulls-eye lesion (5,8,16). Other forms of actinic keratosis, such as hyperplastic keratosis, are more difficult to diagnose with the dermatoscope. Thus, even with the use of non-invasive instrument, it is recommended to conduct pathological examination of skin slices in case of actinic keratosis (1,8,18) (Figure 1). Actinic keratosis is more common in the face, neck, arms, auricles, forearms and top of the head, where sunlight exposure is frequent (1,3). 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 (20,21). Dermatologists can use dermoscopy or a skin slice through the lesion to diagnose AK (Actinic keratosis). General physicians can rule out malignant skin diseases through history taking and physical examination. Early referral to a dermatologist is recommended if the lesions are irregular or unresponsive to skin ointment therapy.

**Clinical course and pathogenesis of Actinic keratosis and prognosis**

The clinical significance of actinic keratosis is that the earliest sign of skin squamous cell carcinoma in situ visible to the naked eye (3,12,19). Approximately 10% of actinic keratosis 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 actinic keratosis (1,8,20). Moreover, 97% of skin squamous cell carcinoma at the site of sun exposure will continue to develop more actinic keratosis around it. When the skin shows actinic keratosis, it is the sign of carcinogenesis, as it has changed from a potential lesion into a clinical certainty, and if left untreated, it will progress to fatal condition of squamous cell carcinoma (7,19,20). At this time, the exposed skin will have accumulated many potential skin cancer stem cells, which will eventually develop into clinically observable skin cancer in the future. Without treatment, the cancer cells will proliferate. Thus, early diagnosis and treatment by clearing the potential surrounding lesions, as well as routine follow-up on the disease, are extremely important (20).

**Treatment of** **Actinic Keratosis**

Conventional treatment involves cryotherapy, electrocautery, laser or surgical resection.

Electric curettage therapy are rarely used at present, but a small number of patients are still more suitable for this invasive method. 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). The lesions of actinic keratosis 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-directed therapy and field-directed therapy (8,10,17).

1.Lesion-directed therapy:

The options of treatment for clinically visible lesions of actinic keratosis 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 (8).

2.Field-directed therapy:

The target of the treatment of actinic keratosis is not only the lesions that are clinically visible to the naked eye, but also the preclinical latent lesions in the area. The objective is to prevent these latent cancer cells from developing into clinically visible precancerous lesions, which will be of considerable benefit to the decline in the prevalence of actinic keratosis and skin squamous cell carcinoma. This type of therapy requires a comprehensive planning and an objective evaluation of the therapeutic outcome (by using a dermatoscope to follow-up regularly).

Currently, there is no standard treatment of actinic keratosis, due to the degree and the depth of the early stage of carcinogenesis of the skin cells. If the patient has only a single lesion, lesion-directed therapy is often the primary choice. If the condition involves multiple lesions of different severity, it is recommended to first perform a lesion-directed therapy to obliterate any apparent lesions before proceeding to other therapies. Liquid nitrogen cryotherapy is most commonly used. Other methods, including electrocautery, laser or surgical resection are also used. The characteristics of these lesion-directed therapy area that the lesions are removed quickly but generating more pain and scars for the patient. Photodynamic therapy is used in the United States and the European Union to treat actinic keratosis, since it is considered the first-line treatment for skin cancer in situ and a variety of superficial skin cancers (17). It is more common in individuals with white skin and more patients are developing skin immunosuppression problems (12). Actinic keratosis may spontaneously regress, remain stable, or turn into aggressive squamous cell carcinoma. With age, large areas of skin are constantly exposed to more ultraviolet rays, especially the head, the neck and the forearms. Current therapies include cryotherapy or resection of lesions, as well as some topical skin ointments such as 5-Fluorouracil, Imiquimod, Diclofenac, and Ingenol mebutate (methanolic extract of Euphorbia peplus) (3,8). Advantage and disadvantage of Actinic Keratosis treatment (Table 1). Various treatment modalities have their advantages and disadvantages, and clinicians should use shared decision making to discuss with patients. The choice of treatment is mainly based on the patient's economic factors, aesthetic factors, or prognosis, etc.

**Prevention of Actinic Keratosis**

Asymptomatic actinic keratosis is often ignored, but as the patient starts to experience pain, itchy or tingling sensation with developing red lesions, they are symptoms of inflammatory actinic keratosis, which are the warning signs to the beginning of progression to skin squamous cell carcinoma (4,12). Thus, it is critical to intervene early at this stage of inflammatory actinic keratosis. Long-term excessive exposure to UVB damage causes microscopic lesions of keratinocytes in the skin, which will eventually turn into skin lesions in old age, commonly seen as actinic keratosis (precancerous lesions), squamous cell carcinoma, basal cell carcinoma, etc (3,4,10).

**Conclusion**

Actinic keratosis 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 (15). Although the dermatoscopy is a good non-invasive approach, the skin biopsy is still the gold standard for clinically confirmed diagnosis. However, given the role of actinic keratosis in skin cancer, further skin biopsy is necessary if suspected. Actinic keratosis is a multi-stage lesion in which the skin is irradiated by ultraviolet light and becomes cancerous by progressing to squamous cell carcinoma. The ultraviolet-induced process involves the accumulation of genetic mutations over several stages, including initiation stage, promotion stage, progression stage, and metastasis (1). It is even possible for the abnormal cancer stem cells to have gradually accumulated in the basal layer of the epidermis before manifesting the clinical appearance of visible lesions. When these abnormal cells reach a certain quantity, they have formed the earliest detectable skin cancer, which is called actinic keratosis. 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.

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Figure 1. Clinical presentation of a actinic keratosis on the back of a 94-year-old woman, and the lesion is 1x1 cm2.



Figure 2. Clinical presentation of a actinic keratosis on the haed of a 94-year-old woman, and the lesion is 1x1 cm2.

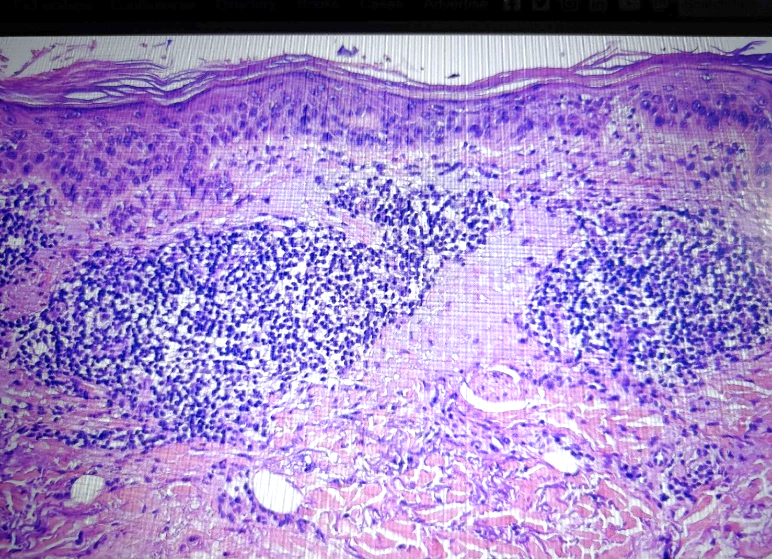


figure 3. H&E stain of histopathological sections of skin.

**Table 1**. Advantage and disadvantage of actinic keratosis treatment

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|  | Advantage | Disadvantage or side effect |
| Cryotherapy | Cryotherapy is the most common treatment | blisters, scarring, changes to skin texture, infections and changes skin color |
| Electrocautery | Electrocautery is safe and effective method | infections, scarring and changes in skin color of the affected area |
| Laser | Lase can reduced collateral tissue destruction, decreased bleeding, shorter healing time, and less scarring | scarring and discoloration of the affected skin |
| Surgical resection | Surgical resection has the highest cure rate of all current treatments | infections, scarring of the affected area |
| Photodynamic therapy | Photodynamic therapy has not long-term side effects and less invasive than surgery, and takes only a short time of treatment | redness, swelling and a burning sensation during therapy |