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Current Concepts In Diagnosing And Treating Actinic Keratosis

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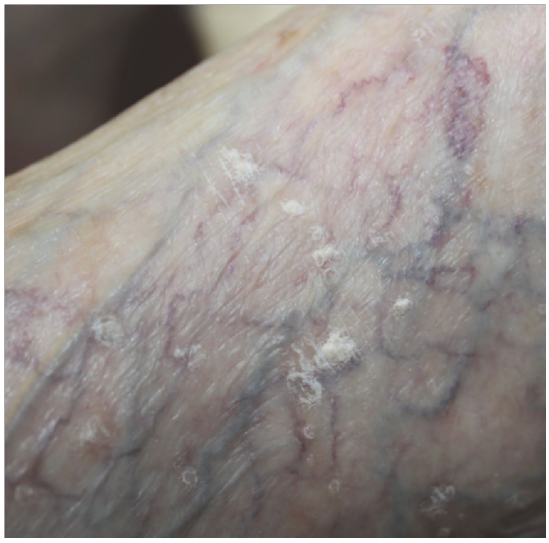
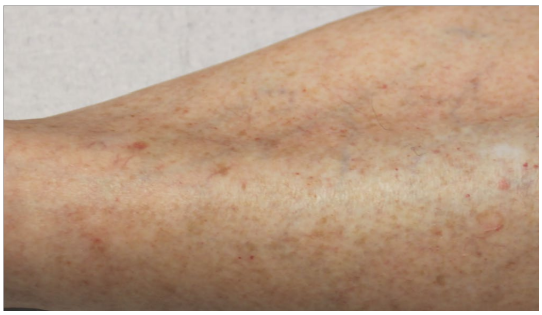
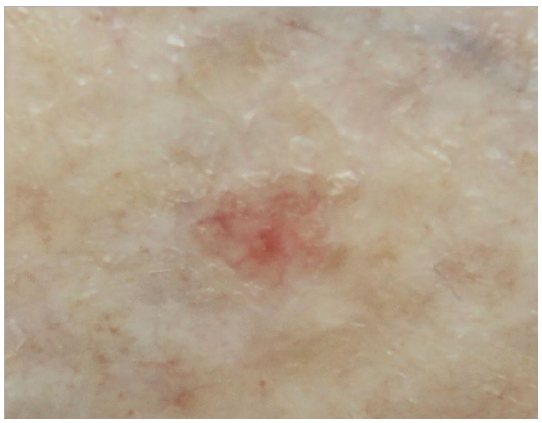
By Myron Bodman, DPM

Given the common nature of actinic keratosis, increasing incidence in older patients and the potential risk of progressing to squamous cell carcinoma, this author reviews risk factors, essential diagnostic considerations and the latest study findings on treatment.



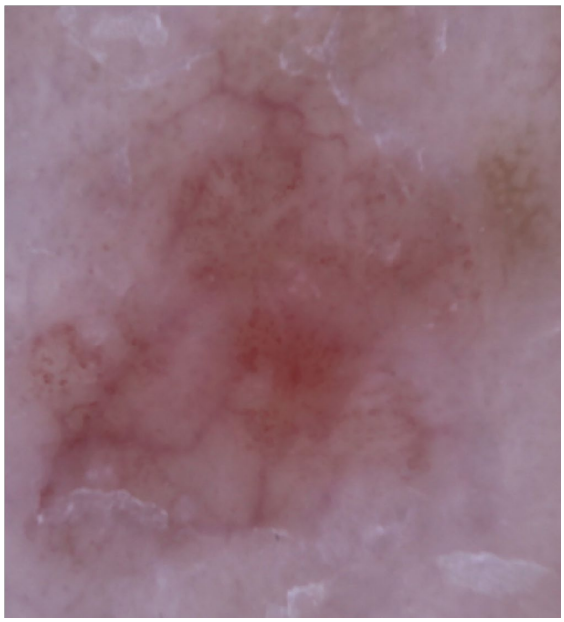


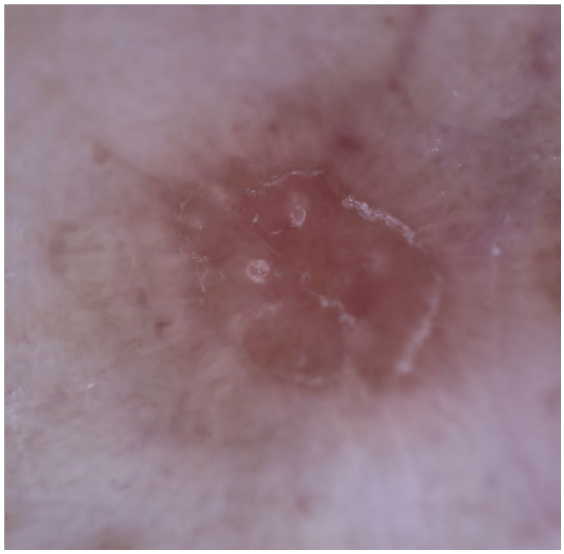


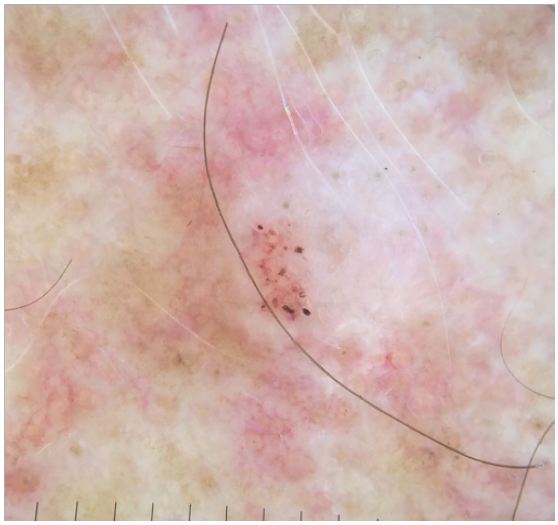
Actinic keratoses (AKs) are pre-cancerous lesions that are easy to detect, diagnose and manage once one has a strong understanding of their clinical features and appropriate treatment options. Although most actinic keratoses occur on arms, recognizing these lesions on the lower extremity helps us prevent squamous cell cancer while educating our patients to take measures to prevent skin cancer. The lower extremities are certainly not free of these premalignant

lesions. Preventing skin cancer is certainly worth our time and e ort to help reduce morbidity and even mortality from nonmelanoma skin cancer.[1]

An actinic keratosis is an early epidermal cancer in situ that can progress to invasive squamous cell carcinoma (SCC).[2] Actinic keratoses are one of the most common dermatological diagnoses worldwide, especially among the elderly, fairskinned and immunocompromised populations.[3] Actinic keratoses have been diagnosed in more than 47 million visits to dermatologists over a 10year period, accounting for 14 percent of all visits to a dermatologist.[1] Actinic keratoses stem from the growth of atypical epidermal keratinocytes). These solar-induced keratoses represent the earliest detectable lesions on a clinical continuum from sun damage to squamous cell carcinoma.[4]







In the United States and Europe, the proportion of adults with actinic keratoses ranges from 11 to 26 percent but is up to 40 percent in Australia.[5,6] A recent study of actinic keratosis prevalence in Baltimore by Yaldiz found a steadily increasing prevalence with age.[7] Patients in their 30s had a prevalence of only 0.01 percent while the prevalence reached 9.38 percent for patients in their 70s and 14.57 percent for patients over the age of 80.[7]

It is important to remember that ultraviolet light induces mutations in the tumor suppressor gene p53 and this suppression of surveillance is a very common pathway to many human cancers. These mutations are present in more than 90 percent of squamous cell carcinomas and are also usually found in actinic keratoses.[8] It is thought that the mutated cells expand preferentially in a clonal fashion at the expense of the normal surrounding keratinocytes to develop into a clinical lesion of an actinic keratosis.[8]

What Risk Factors Predispose Patients To Actinic Keratoses And Skin Cancer?

Individuals with extensive sun exposure are at increased risk of developing actinic keratoses. In a population-based study in the United States of patients with a high cumulative sun exposure, actinic keratoses were present in 55 percent of Caucasian men and 37 percent of Caucasian women between the ages of 65 and 74 years.[9]

The lower extremities are especially common sites for actinic keratoses to develop in women. Skin adjacent to actinic keratoses usually show signs of solar damage, such as a yellow or pale discoloration, spotty hyperpigmentation, scattered telangiectasias or xerosis.[4] Actinic keratoses are generally asymptomatic but some patients report local tenderness or even a stinging sensation.[4]

A history of sunburns increases the risk for the development of actinic keratoses. In an Australian study, six or more painful sunburns over the course of one’s life were associated with an increased likelihood for actinic keratoses.[5] A study performed in Queensland, Australia found that even a single episode of sunburn during childhood was strongly associated with the development of actinic keratoses.[10]

Actinic keratoses are uncommon in African-Americans. Melanin works well to absorb damaging ultraviolet radiation and shields dividing keratinocytes, resulting in reduced risk for actinic keratoses in those with darker skin pigmentation.[4] Melanin acts as an ultraviolet sun shade. Patients with an increased risk of actinic keratosis often have skin with many freckles, light hair color, a history of frequent sunburns and lack an ability to tan.[4]

Gender is also a risk factor for actinic keratosis development. In general, men are more likely than women to develop these lesions. But interestingly, elderly women who grew up in the southern United States and wore skirts or dresses are at higher risk for actinic keratoses and squamous cell carcinoma on the anterior shins because of the increased localized sun exposure.[11] The prevalence of actinic keratosis rises with age and an overall accumulation of sun exposure.

Interestingly, a history of long-term systemic voriconazole (Vfend, Pfizer) therapy, which physicians frequently administer for candidemia or aspergillosis infections, often triggers gradual development of squamous cell carcinoma.[12] After six months of a patient taking voriconazole, one may note the development of acute photosensitivity and photoaging that is followed within three years by an increase in actinic keratoses that lead to squamous cell carcinoma.

Mastering The Clinical Evaluation Of Actinic Keratosis

Actinic keratoses begin as erythematous and scaly macules or papules. The lesions are most common in adults with Fitzpatrick type 1 skin (always burns, never tans). Clinicians frequently find actinic keratoses on sun-exposed areas of the legs and arms, and especially the balding scalp, face, and lateral neck.[4]

As time and sun exposure progresses, the actinic keratosis papules enlarge into elevated plaques that are easily palpable. The classic form of actinic keratosis presents as plaque that ranges from a few millimeters to two centimeters in diameter. Hypertrophic varieties of actinic keratoses are characterized by the presence of thick, adherent scales on an erythematous base. When it comes to the atrophic type of actinic keratoses, scale is absent and the lesions present as smooth, red flat macules.[4] It is easy to confuse these presentations with a variety of common cutaneous disorders.

Can dermoscopy help in the diagnosis of actinic keratosis? The non-invasive dermoscopy examination has proven to be an increasingly useful instrument in the podiatrist's diagnostic tool chest. In order to distinguish actinic keratosis from benign melanocytic nevi, xerosis, verrucae or psoriasis as well as squamous cell carcinoma, basal cell carcinoma and melanoma, it is important to recognize the distinctive dermoscopic features of actinic keratoses.

The most easily identified dermoscopic feature of facial actinic keratosis is the "strawberry pattern." The strawberry pattern is a pseudonetwork of dilated vessels on a background of erythema. To explain, the normal reticulated pigment network of skin is usually absent on the face, palms and soles, and in cases of actinic keratosis is replaced by a pseudonetwork on the face and parallel pigment patterns on acral skin.[13,14] The vessels can be linear or wavy. If present, hair follicles may appear to be dilated with a white halo. Pigmented actinic keratoses are typically slate-gray to brown dots and globules around hair follicles.[4]

Identifying The Key Differential Diagnoses

At the top of the list of differential diagnoses of actinic keratosis is squamous cell carcinoma. Both actinic keratosis and squamous cell carcinoma lesions often begin as erythematous, scaly patches on sun-exposed skin. If the lesion is growing rapidly, tender or ulcerated, a biopsy is recommended.

The differential diagnoses for actinic keratosis would also include benign lichenoid keratoses. These lesions look similar to nummular eczema with a well-defined border of solid erythema and scale. One should also consider superficial basal cell carcinoma. It presents as a scaly, pink to red-brown patch and is predominantly located on the trunk. Superficial basal cell carcinomas typically will have shiny white-to-red areas, erosions and short, fine, polymorphous telangiectasias. They typically have polymorphous vessels that are dotted, glomerular or linear in appearance.[15]

Also consider the common seborrheic keratosis, which can resemble actinic keratosis with a warty, scaly, “stuck-on” appearance in sun-exposed areas. Seborrheic keratoses often start as light brown, oval macules that progress into sharply demarcated bordered plaques with a waxy, “stuck-on” appearance. Evaluation with a dermatoscope can aid in detecting the round, bright yellow-brown, milia-like cysts in pigmented seborrheic keratoses.

Finally, a list of actinic keratosis di erentials should also include porokeratosis of Mibelli, which, like actinic keratoses, is a precancerous lesion, which can also occur on the lower legs. Porokeratosis of Mibelli typically presents as multiple, bilateral, larger lesions with characteristically palpable rims and flat, atrophic centers.

Addressing Biopsy And Classification Of Lesions

Clinicians often initially diagnose actinic keratoses via the clinical examination but the gold standard of diagnosis is biopsy with histopathological analysis. Biopsy is recommended if the actinic keratosis recurs after treatment or fails to respond to treatment. Typically, a simple shave biopsy will suffice.

Histologically, actinic keratoses are usually divided into five different varieties: hypertrophic, atrophic, Bowenoid, acantholytic and pigmented.[8] The hypertrophic and atrophic types are the most common variants. Characteristic histological features of hypertrophic actinic keratosis include hyperkeratotic stratum corneum, pronounced orthokeratosis intermingled with parakeratosis (the “flag sign”), hypergranulosis, acanthosis and dysplasia of the lower epidermis.[8,16,17]

Once one has made the diagnosis, the clinician can stratify and grade individual actinic keratosis lesions by their severity to help guide specific treatment selection. Grade 1 lesions are slightly palpable and more easily felt than seen. Grade 2 lesions are moderately thick actinic keratoses that are easy to see and feel while grade 3 actinic keratoses are very thick and/or hyperkeratotic.[18]

Pertinent Pearls In Managing Actinic Keratosis

Evaluating the grade of severity of the patient's actinic keratosis helps guide optimal treatment decisions. Kircik makes an important point that patients often present with a spectrum of grades of multiple actinic keratoses on the anterior shins and dorsal feet.[19] According to Kircik, when it comes to patients having multiple actinic keratoses on the shins, one could most accurately describe this as "field disease" or "field cancerization" with a mix of clinical and subclinical lesions present in the same region.
Topical diclofenac 3% in a 2.5% hyaluronan gel is a good therapeutic option for patients with actinic keratoses. However, the use of this medication is limited due to low e icacy in comparison with other topical treatments and a prolonged treatment course (twice a day application for 60 to 90 days). The most common adverse e ects of diclofenac gel are dry skin, pruritus, erythema and, rarely, a rash at the application site.[4,20]

Dermatologists often prescribe topical fluorouracil but it can cause significant inflammation and lesion necrosis. Patients would apply fluorouracil 5% cream once or twice daily for two to four weeks until superficial erosion occurs. To improve a patient's adherence to treatment, some clinicians utilize topical corticosteroids to reduce the inflammatory response associated with treatment.[4] Fluorouracil cream causes inflammation and lesion necrosis by inhibiting DNA synthesis. It typically takes four to six weeks for the skin to progress through erythema, blistering, necrosis with erosion and reepithelialization. In patients with extensive actinic keratoses, the treated area may become extremely inflamed.[4]

In the past, destruction of lesions and biopsy were the most frequently performed procedures to treat actinic keratoses.[1] Historically, radiation to skin cancers for the lower legs has been avoided due to a perceived increased risk of radiation toxicity. Radiation can cause poor wound healing and radiation necrosis. For patients not eligible for surgery, radiation therapy is an option with a complete response rate of 65 percent and a 17 percent risk of poor wound healing or radiation necrosis.[21]

Researchers have reported that photodynamic therapy is well-tolerated and produces favorable cosmetic outcomes.[18] Phototoxicity reactions essentially resolve one month after treatment. In a recent review, Vale and colleagues found that Ingenol mebutate (Picato®, LEO Pharma), the newest but most expensive topical field therapy, 5-fluorouracil and photodynamic therapy were the most cost-e ective treatments for actinic keratoses.[3]

In a recent randomized trial involving 600 patients with multiple contiguous actinic keratoses, Jansen and colleagues noted that topical fluorouracil resulted in higher rates of treatment success at 12 months in comparison to imiquimod, methyl aminolevulinate, photodynamic therapy or Ingenol mebutate.[22]

What may the future hold for actinic keratosis treatment? Clinical trials are currently underway to investigate modalities such as proapoptotic, immunomodulant and chemopreventative agents. Eflornithine (Vaniqa®, Allergan), nicotinamide, perillyl alcohol and liposomal molecules are currently in the midst of phase II trials.[23]

Active Treatment Or Simple Surveillance?

There is controversy regarding active treatment of actinic keratoses versus simple surveillance. Jansen and team note that "although many patients may benefit from treatment of actinic keratosis because of the decreased risk of progression to squamous cell carcinoma, active surveillance can be an alternative."[24] Prospective studies, in which the estimated percentage of actinic keratosis lesions that progress to squamous cell carcinoma is 0.1 percent per lesion per year, have shown that many cases of actinic keratosis regress spontaneously and 40 percent of squamous cell carcinomas arise in clinically normalappearing skin.[25] Active treatment is more likely to occur in a patient-centered health care system while simple surveillance might be an approach favored in a more socialized health care system.

Educating Patients On Actinic Keratosis Prevention

Sunscreens have been shown to not only reduce the development of actinic keratoses but heal existing ones. In a randomized controlled trial conducted in Australia, over 500 residents who already had actinic keratoses were divided into a sun protection factor (SPF) 17 sunscreen group and a vehicle-only group.[26] Over seven months, the sunscreen group developed less than half the actinic keratoses than those reported in the vehicle-only group. In addition, there were significantly more remissions of actinic keratoses in the sunscreen group.
According to Allen and colleagues, cancers that occur on the dorsum of the foot are associated with ultraviolet light exposure and are thus preventable.[27] The dorsum of the foot is of particular interest because it can often become unprotected in beachgoers, triggering sunburn and increasing the risk of development of skin cancer. Unfortunately, surveys find that of all body sites, the dorsal aspect of the feet are the least likely sites to receive sunscreen applications.[27] Simply wearing shoes and socks may be an even better photoprotective measure for feet.

Final Thoughts

In summary, educating our patients to use sunscreens and protective clothing are important public health measures to recommend. Learning to detect precancerous actinic keratoses and managing them appropriately should help reduce skin cancer complications and provide more comprehensive care for our patients.

Dr. Bodman is a retired Associate Professor with the Kent State University College of Podiatric Medicine. He is board-certified by the American Board of Podiatric Medicine.

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