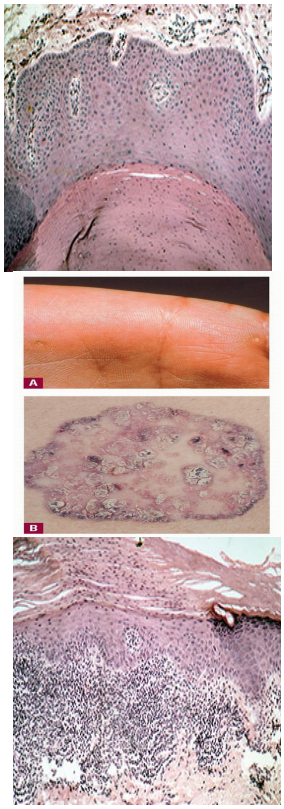

ARSENICAL KERATOSES

Arsenical keratoses (ArKs) are precancerous lesions found in association with chronic arsenicism. These lesions have the potential to develop into invasive SCC. Arsenic is a ubiquitous element that has no color, taste, or odor. It has the potential to cause characteristic acute and chronic syndromes in persons exposed to it, and such exposures are typically obscure because medicinal, occupational, and environmental sources exist. Detection of acute and chronic arsenicism is important, because the acute form can be fatal and the chronic form is associated with a variety of cutaneous and internal malignancies. ArKs are associated with chronic arsenicism.

Epidemiology

Knowledge of the medicinal benefits and poisoning potential of arsenic dates back to ancient times. Arsenic was introduced into the United States Pharmacopoeia in 1850, and before its use was discontinued around 1965, it was employed medicinally in the United States and Europe in the form of Fowler's solution, Donovan's solution, and Asiatic pills for treatment of various illnesses such as psoriasis, asthma, and syphilis. Medicinal exposure is now basically limited to treatment of tropical diseases, such as African trypanosomiasis, and more recently to treatment of various hematologic malignancies.[67] Arsenic in opium has been and is still used for medicinal and recreational purposes in India, and inorganic arsenic is still found in some traditional Chinese herbal preparations. [78] Unfortunately, these substances can be easily purchased and are increasingly being used again as homeopathic remedies, which results in modern day cases of what once was primarily a disease of historical interest.

Arsenic exposure can occur in a variety of occupations, either by direct exposure to arsenic or through indirect exposure from contaminated water and landfills. In 1973, it was estimated that more than 1.5 million workers in the United States were potentially exposed to arsenic in the workplace.[79] Occupations that carry risk of exposure include jobs in the mining, smelting, agricultural, computer microchip, forestry, electroplating, semiconductor, and glassmaking industries. Environmental exposure is often obscure and insidious, because there may be latent periods of up to 50 years before manifestations of chronic arsenicism appear. Arsenic is routinely found in soil, and it is found in much higher levels in the well water of certain regions where smelting and mining activities predominate, such as Taiwan, Sweden, and Argentina. [78]

Other routes of environmental exposure include some illegally produced alcoholic beverages and the burning of pressure-treated lumber that has been pretreated with chromated copper arsenate. In all forms of medicinal, occupational, and environmental exposures, longer duration of exposure and higher cumulative dose are associated with a higher risk for the development of ArKs.

History

Etiology and Pathogenesis

Arsenic is present as either organic or inorganic compounds as well as in three potential oxidative states: metalloid, trivalent, and tetravalent. Trivalent arsenicals are the most common and hazardous to humans. The toxicity of these compounds depends on the accumulation of arsenic in target tissues and its metabolism and elimination. Organic arsenicals are excreted rapidly. Trivalent inorganic arsenicals are the most acutely and chemically toxic compounds. Because arsenic is metabolized and detoxified in the liver via methylation, patients

with pre-existing liver disease may be at greater risk for arsenic-related toxicity.

The mechanisms of arsenic-induced keratoses and malignancy are not fully understood. Arsenic reacts with the sulfhydryl groups in certain tissue proteins and subsequently affects many different enzymes that are essential to cellular metabolism. Arsenic has been found to cause chromosomal mutations, chromosomal breaks, sister chromatid exchanges, and mutations in

Clinical Findings

ArKs typically begin as pinpoint papules that are more easily felt than seen. They develop into small, 2- to 10-mm, punctate, yellow, keratotic papules most commonly seen on the palms and soles in areas of constant pressure or repeated trauma . They preferentially arise on the thenar and lateral borders of the hands, the sides of the fingers, and sometimes on the dorsal aspects of the fingers, overlying the joints. Although it is unusual, ArKs can be found on more widespread body areas such as the trunk, extremities, eyelids, and genitalia. ArKs may also present as slightly elevated, erythematous, scaly or pigmented plaques. ArKs on the palms and soles are more likely to be seen in individuals with chronic arsenicism caused by medicinal exposure than in those with arsenicism due to occupational exposure. Also, individuals with arsenical-related cancer are more likely to have palmar and plantar ArKs. The mean latency

period for the development of ArKs varies considerably from 9 to 30 years.

Other cutaneous neoplasms associated with chronic arsenicism include BD or SCC in situ, SCC , and BCC . Mean latency periods for the development of BD and SCC can also be as long as 40 years.[85] With arsenic as the carcinogen rather than UV radiation, these neoplasms, like ArKs, are distributed in more widespread, random, and nonphotodamaged areas. Arsenical BD often begins as a small flesh-colored to pink papule with a thick horny layer or crust. When this crust is removed, the underlying skin appears erythematous and oozing. Over time, unlike the relatively stable ArKs, these lesions increase in size, forming nodular and plaque-like lesions that often group together. Approximately one-third of patients have multiple lesions of BD.

Arsenic-induced BCCs are also usually multiple, and the majority are of the superficial type, although small nodular BCCs are sometimes seen. These BCCs are found in a random, scattered distribution, primarily on the trunk and in hair-bearing regions. Clinically, the superficial BCCs are often indistinguishable from BD. Arsenic-related SCC can arise de novo or from malignant transformation of ArKs and BD lesions. In one study, 55 percent of SCCs arose from pre-existing ArKs or BD lesions. Patients with SCC are more likely to have been exposed to arsenic earlier in life than are those without SCC. They also are more likely to have multiple lesions of BD and more numerous palmar and plantar ArKs. The majority of SCCs have been found on the distal extremities of the hands and feet, and it has been hypothesized that irritation and trauma in these areas may increase the risk of malignant transformation. Clinically, ArKs that show progression to SCC often present with pain, bleeding, fissuring, and later ulceration. They tend to gradually expand in diameter, forming a large erosion or ulceration, and they sometimes reach sizes of up to 20 cm.

Other signs of chronic arsenicism include hyperpigmentation primarily affecting the nipples, axillae, groin, and other pressure points. Within these hyperpigmented patches are often seen small areas of hypopigmentation, resembling “raindrops in the dust.” Diffuse alopecia of the scalp may be present. Longer term, patients may develop “blackfoot disease,” which is a peripheral vascular disorder affecting the lower extremities that eventually results in gangrene. Hepatic cirrhosis can also occur. A variety of internal malignancies have been associated with chronic arsenicism, with long lag periods of 20 to 50 years reported. The internal malignancies linked with chronic arsenicism include lung, urinary tract, and hepatic tumors, hepatic angiosarcoma, leukemia, and lymphoma.

Histopathology

The histopathologic features of ArKs are essentially the same as those of AKs. No reliable histopathologic criteria can distinguish between the two. Some cases of ArKs are characterized by marked vacuolation of the epithelial cells and keratin horn formation. Also, solar elastosis is usually absent, and a chronic dermal lymphocytic infiltrate is commonly seen. Likewise, arsenic-related BD, BCC, and SCC are histopathologically indistinguishable from their non-arsenic-induced counterparts.

Diagnosis and Differential Diagnosis

ArKs may be mistaken for other types of punctate keratoses, such as disseminated punctate keratoderma, Darier disease, corns, and verruca vulgaris. Disseminated punctate keratoderma usually appears earlier in life. It has also been reported that on removal of the keratinous plugs in punctate keratoderma, small crater-like pits are left behind, whereas no pits are seen on removal of the keratin plugs in ArKs. Darier disease presents with characteristic lesions elsewhere. Corns are usually not so numerous and not so common on the hands. Warts often demonstrate evidence of thrombosed capillaries on removal of the surface keratin.

A diagnosis of ArKs and chronic arsenicism should be considered when numerous characteristic keratoses are seen on the palms and soles or when multiple lesions of BD, SCC, or BCC are found on an individual, especially when these lesions are in non-sun-exposed regions of the body. In most patients with

such neoplasms, palmar and plantar keratoses will also be present. Such patients should be questioned about previous occupations, living conditions, and environmental and medicinal exposures to elicit a history of potential arsenic exposure anywhere from 10 to 40 years previously. Biopsy of any changing ArK or erythematous nodule or plaque on the body should be performed to ensure that BD, BCC, or progression to SCC is not present.

Prognosis and Clinical Course

ArKs and arsenical-induced BD tend to persist for many years, and progression to invasive SCC is believed to be relatively rare. Invasive SCCs that arise in ArKs, however, are more locally aggressive and have a greater chance of metastasis than SCCs arising in AKs. In lesions of

arsenical-induced BD, locally invasive SCC has been seen histopathologically in up to 20 percent of cases. Once invasive SCC has occurred in BD, it is said that at least one-third will demonstrate evidence of metastasis unless adequate treatment is provided.[86]

Treatment

Management of patients with chronic arsenicism and ArKs should include regularly scheduled total-body skin examinations and general physical examinations, possibly every 6 months.[85] The exact incidence of internal malignancies associated with chronic arsenicism is unknown, so there is no standard protocol for the evaluation of potential internal malignancies. Exhaustive evaluations to detect such malignancies have not been recommended. Biannual detailed history taking and physical examination, yearly chest radiography, and selective testing when clinically indicated are probably reasonable recommendations.

Treatment of ArKs likewise is not standard and not mandatory, although treatment of these lesions is sometimes initiated to relieve the associated discomfort that some patients experience. Available localized treatment options include surgical excision, cryosurgery, curettage with or without electrocautery, CO_2 laser treatment, and topical chemotherapy with 5-FU, although 5-FU therapy is less successful in treating ArKs than in treating AKs. PDT with ALA has also been used to treat these lesions. Oral retinoids may be useful in reducing the hyperkeratosis associated with ArKs. One can assume that imiquimod may be effective, but there are no studies of its use to date.