

Arsenic and skin cancer – Case report with chemoprevention

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ABSTRACT

Introduction: Arsenic is a potentially hazardous metalloid that can cause skin cancer. We want to demonstrate a case of chronic arsenicosis and the potential of chemoprevention with retinoids. **Case Report:** This is a case report of a 72-year-old male patient who was exposed to arsenics by dust and direct skin contact over 3 years in a chemical plant in the late forties. He developed multiple arsenic keratosis clinically resembling actinic keratoses, Bowen's disease and palmar minute keratoses. To prevent a transformation into invasive cancer and to lower the burden of precancerous and in situ cancer lesions, he was treated orally with acitretin 20 mg/day. During 9 months of chemopreventive retinoid therapy a partial response of pre-existent skin lesions was noted. Treatment was well tolerated. During follow-up of 5 years no invasive malignancy developed. **Conclusions:** Intense exposure to arsenics during a relatively short period of 3 years bears a life-long health hazard with the delayed development of multiple in situ carcinomas and precancerous lesions. Chemoprevention with retinoids can induce a partial response.

Key words: Arsenics; Metalloids; Occupational hazards; Multiple Bowen's disease; Minute keratoses; Arsenic keratoses

INTRODUCTION

Arsenic is an ubiquitous metalloid which poses health risks for humans. Typical non-occupational and occupational sources of exposure are summarized in Table 1. Chronic exposure possess an increased risk for lung and bladder cancer [1,2].

Arsenic is a primary carcinogen in the skin following ingestion or topical exposure. Chronically exposed patients develop mainly precancerous arsenic keratosis, but in situ carcinoma (Bowen's disease and actinic keratosis) and invasive basal or squamous cell carcinoma have also been observed (Table 2) [3].

There is a number of occupational studies demonstrating a high risk of lung cancer related to arsenic exposure by inhalation. There is less data available on the possible association of occupational arsenic exposure with nonmelanoma skin cancer (NMSC). Recent studies suggest arsenic exposure

increases the risk of NMSC as a cofactor to smoking and sunlight exposure [4,5].

The pathways by which arsenic is inducing skin malignancies are yet only poorly understood. In cell culture and animal models cytotoxicity leading to increased but disturbed repair activities have been observed. A number of proinflammatory cytokines are released by cells exposed to arsenic including tumor growth factor- α . In animals no skin cancer was induced by arsenic. Arsenic is capable to induce post-translational histone modifications that may induce global transcriptional repression including tumor suppressor genes [6,7].

CASE REPORT

A 72-year old Caucasian man presented with multiple keratoses and pits on his palms for years ago. The patient had no history of a familial occurrence of such cutaneous signs. He was not under immunosuppression

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Table 1: Exposure to arsenic

Non-occupational	
Drinking water	
Food	
Betel quid chewing	
Chinese traditional medicine	
Occupational	
Miners	
Metallurgy workers	
E-material recycling workers	
Farmers and tree planters exposed to fertilizers	
Cooking plant workers	
Outdoor workers exposed to urban air pollutants	
Wine makers (and drinkers)	

Table 2: Cutaneous manifestations of arsenic exposure

Exfoliative dermatitis	Pimparkar & Bhave 2010
Hyperkeratosis	Pimparkar & Bhave 2010; Wong et al. 1998
Vitiligo	Pimparkar & Bhave 2010; Hall 2002
Spotted melanosis	Hall 2002
Mee's lines on nails	Hall 2002
Bowen's disease [12,20,21]	Yahya & Mohammed 2005; Lee & Bebb 2005; Wong et al. 1998
Basal cell carcinoma [12,22]	Koc et al. 2014; Wong et al. 1998
Squamous cell carcinoma [12,23,24]	Elmariah et al. 2008; Mitropoulos & Norman 2005; Wong et al. 1998

nor had he received an organ transplant. His Fitzpatrick skin type was III. He reported that the lesions developed over four decades. His own medical history was unremarkable.

A thorough clinical examination and a skin biopsy were performed. On his palms small pits were found (Fig. 1). Nails, hair, teeth and oral mucous membrane had no pathologic symptoms. We observed more than 100 hypertrophic keratoses and Bowen's disease randomly distributed over the whole body except his face (Fig. 2). These lesions in conjunction with the pathological report suggest a chronic arsenic intoxication. On request it became clear that he became exposed to arsenics (arsenites and arsenates - dust and direct skin contact) during an occupation in a chemical plant for several years as war prisoner in the 1940ies (1945-1948). After his war prison years he was neither an outdoor worker nor a smoker.

First dermatological consultation was recorded in 1988.

During follow-up over 5 years, several lesions have been removed over time under the suspicion of an early invasive squamous cell carcinoma what could be excluded by histopathology.

There was no development of internal cancer such as lung or bladder cancer.

**Figure 1:** Palmar hyperkeratosis with minute pits.**Figure 2:** Multiple keratosis (Bowen's disease) on trunk (and extremities).**Figure 3:** (a) Actinic hyperkeratosis before chemoprevention with acitretin, (b) Partial remission after 9 months of oral acitretin therapy.

He had neither a peripheral neuropathy nor cardiac arrhythmias. Laboratory test for plasma arsenic concentration of 24h-arsenic excretion were not performed since the exposure was decades ago. The diagnosis of chronic arsenicosis was made by medical history, clinical examination and histopathology of selected lesions. Histologically Bowen lesions and hypertrophic keratoses with atypical epidermal keratinocytes were observed.

He was given oral acitretin 20 mg per day as a chemopreventive measure for 9 months. The treatment was well tolerated under strict laboratory control. A partial regression of lesions was seen but not complete remission was achieved (Figs. 3a and b). On the other hand, no progression to invasive skin cancer has been observed.

DISCUSSION

Chronic arsenic exposure poses a health risk for the whole life [8-10]. Skin lesions like palmar pits, multiple keratoses and multiple Bowen's lesions on sunprotected skin are biomarkers for chronic arsenic exposure [11]. The development of precancerous lesions and in situ skin cancer is well known in the medical literature (Table 2) [3,10,12]. Invasive skin cancer such as basal cell carcinoma or squamous cell carcinoma has rarely been observed. Epidemiologic studies suggest that sunlight exposure and smoking are major factors which may become aggravated by chronic arsenic exposure [1,2]. Although skin carcinogenesis by arsenic is not completely understood, aberrant proliferation, release of proinflammatory cytokines, oxygen radical production, disturbed local immune response including impairment of p53 tumor suppressor function, and aggravation of UVB and UVA procarcinogenic effects have been detected [13].

Arsenite inhibits transcription of signaling kinase genes and downstream DNA repair genes DDB2 and RAD23B. Arsenite can displace zinc from the zinc fingers in proteins involved in DNA repair. These effects likely contribute to decreased nucleotide excision repair [14].

In our case no cofactors of arsenic toxicity (smoking or outdoor work) were evident. Drinking water is not a significant factor of chronic arsenic exposure in the region. So the only factor that could be established was a three year unprotected exposure to arsenics in a French chemical plant after World War II. It is remarkable that a relatively short but intense exposure to arsenics can cause ongoing health hazards. Patients with chronic arsenicosis need a lifelong follow-up since invasive cancer can develop with a delay of decades.

Chemoprevention of arsenic skin cancer has not really been established. In a phase I trial curcumin was applied in doses of 1 to 12 g per day. No toxicities were observed and a mild cancer protective

activity was noted [15]. Other phytochemicals are under investigation [16]. A prospective trial has been initiated in Bangladesh with a 6-year supplementation with alpha-tocopherol (100 mg daily) and L-selenomethionine (200 μ g daily) for the prevention of nonmelanoma skin cancer [17]. The future will show if the promises can be fulfilled.

Long term treatment with retinoids, in particular isotretinoin and acitretin, has shown activity in NMSC [18,19]. Here we could demonstrate a partial remission of hypertrophic arsenic keratoses. If the treatment prevented lung and bladder cancer in our patient would be a matter of speculation only. Nevertheless, oral retinoid chemoprevention can be a measure in high risk patients after chronic arsenic exposure.

Key messages

- Chronic arsenicosis is a life-long disease with the potential of skin, lung and bladder cancer development.
- Symptomatology occurs after a delay of several years or even decades.
- Chemoprevention by oral retinoids is a measure for high-risk patients.
- A lifelong follow-up is recommended.

Consent

The examination of the patient was conducted according to the Declaration of Helsinki principles.

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