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Acral keratoses and squamous-cell carcinomas likely associated with arsenic exposure

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Abstract

Chronic arsenic exposure is known to induce punctate keratoses with an increased risk of primary squamous-cell carcinoma. Drinking water is currently the major source of arsenic exposure worldwide and is considered one of the most substantial environmental carcinogens. We describe the case of a 61-year-old Hungarian woman with scattered, acral, hyperkeratotic papules and a history of five palmoplantar squamous-cell carcinomas as well as two other extremity non-melanoma skin cancers. Prior to immigration, she had lived in a county of Southern Hungary that is known to have elevated concentrations of inorganic arsenic in the drinking water above the World Health Organization's current maximum threshold for safety. To date, this report is the first to describe the phenomenon of palmoplantar squamous-cell carcinomas in a patient from this region and underscores the importance of vigilant screening in those individuals who have spent substantial time in high-risk regions internationally and domestically.

Case Presentation

PATIENT: 61-year-old-woman

DURATION: Eight years

DISTRIBUTION: Hands and feet

HISTORY: A 61-year-old woman presented to Bellevue Hospital Center Dermatology Clinic in January, 2016, with two, painful, hyperkeratotic papules on the feet. The patient had a longstanding history of multiple, punctate, palmoplantar keratoses that had been treated unsuccessfully as dyshidrosis, irritant dermatitis, and verruca vulgaris. In 2008, a biopsy specimen of one of these lesions on the right first finger was consistent with a squamous-cell carcinoma (SCC), later found to be metastatic to an axillary lymph node, status post resection. In 2010, she was diagnosed with SCC of the left foot; in 2011, an SCC in situ of the left thigh; and finally, in 2013, an infiltrating SCC of the left fourth finger. At her initial evaluation, the patient complained of two tender papules – one of the lateral aspect of the left foot and one at the right midfoot. Biopsy specimens both showed



Figure 1. Scattered, hyperkeratotic papules were present on the lateral aspects and plantar aspects of the feet.



Figure 2. Hyperkeratotic papules were present on the lateral aspects and plantar aspects of the feet.

invasive squamous-cell carcinomas. An additional biopsy specimen from the right shoulder was consistent with a basal-cell carcinoma. She took no medications and had no medication allergies. There was no family history of skin cancer.

The patient had emigrated from Hungary in 2006. She was born and raised in Kiskunhalas, which is a city in the Southern county of Bács-Kiskun, where she lived in a family home and had an adequate food supply and clothing, which included shoes. They drank city tap water and did not live near manufacturing plants or factories. The patient worked as a kindergarten teacher while living in Hungary and as a nanny since moving to the United States. She did not have any hobbies that involved chemical exposure but did report prior history of outdoor and indoor tanning (approximately 40 sessions over the course of ten years total). The patient had never smoked and did not drink alcohol.

PHYSICAL EXAMINATION: Scattered, hyperkeratotic papules were present on the lateral aspects and plantar aspects of the feet (**Figures 1 and 2**). Some lesions had crusted, central ulcers. There were similar papules on the fingers. The left foot and right first finger had healed surgical sites. She had no axillary or inguinal lymphadenopathy.

LABORATORY DATA: None

HISTOPATHOLOGY: There is full-thickness keratinocytic atypia (**Figure 3**).

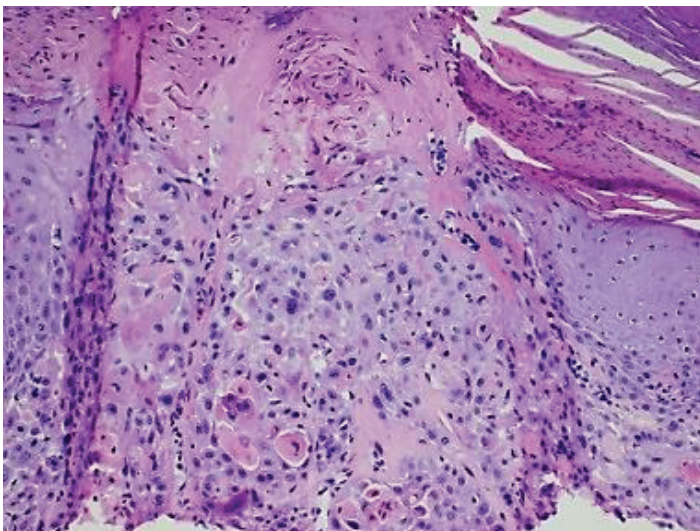


Figure 3. There is full-thickness keratinocytic atypia.

DIAGNOSIS: Acral keratoses and squamous-cell carcinomas likely associated with arsenic exposure

Discussion

Palmoplantar keratoderma (PPK) is a descriptive diagnosis, which often is classified by inheritance—hereditary or acquired—and by pattern of hyperkeratosis—diffuse, focal, or punctate. While the majority of cases are not associated with skin cancer, there are some exceptions [1, 2]. Chronic arsenic exposure is known to induce punctate keratosis, with an increased risk of primary SCC [3–10]. Up to 55% of pre-existing lesions may develop into infiltrative or in situ SCCs, according to a case series from China [9].

Arsenic is an acute and chronic toxicant and carcinogen, [8] which is abundant both naturally and anthropogenically. It gained popularity as a poison beginning in the Roman Empire and was developed for chemical warfare as the vesicant Lewisite (pseudonym Dew of Death) during World War [11]. It also was once used in pharmaceuticals for syphilis, psoriasis, trypanosomiasis, and asthma; wood preservatives; and agricultural pesticides, herbicides, sterilants, and other preparations although many of these agents have been restricted or abandoned due to health concerns [6, 8].

Currently, drinking water is the major source of arsenic exposure worldwide and considered one of the most substantial environmental carcinogens [6, 8]. In 2010, the Joint Food and Agricultural Organization of the United Nations (FAO)/World Health Organization Expert Committee of Food Additives (JECFA) re-evaluated data on the health ramifications of arsenic exposure and revised their safety guideline from 50 $\mu\text{g/L}$ to 10 $\mu\text{g/L}$ [3, 4, 6]. This new level represents a 0.0006 excess risk of skin cancer, which is a factor 60 times higher than that typically used to protect human health. The WHO has since stated that acceptable levels may be as low as 0.17 $\mu\text{g/L}$, which were previously below the threshold for analytic detection [3].

Unfortunately, the replacement of surface wells with groundwater sources to limit microbial contamination unexpectedly exposed millions of

people to levels of inorganic arsenic that exceed the JECFA guideline [3, 6]. Regions at particular risk include: Bangladesh, China, West Bengal, and smaller areas in Argentina, Australia, Chile, Mexico, Taiwan, the United States, and Vietnam [3, 4, 6-8]. More recent data from the European Union-sponsored Arsenic Health Risk Assessment and Molecular Epidemiology (ASHRAM) study as well as other groups suggest that several counties in Hungary, which include Bács-Kiskun where our patient lived, also rely on water sources, which contain high levels of arsenic, and that this consumption correlates with elevated urinary concentrations, which is a metric for possible toxicity [5,12-14].

Despite this epidemiologic information, there are few reports that evaluate arsenic consumption and the development of skin cancers in individuals from Hungary. A single study showed a dose-response increase in the risk of basal-cell carcinoma (relative risk 1.18, 95% confidence interval 1.08 to 1.28 for each 10 µg/L increase in average lifetime drinking water concentration), [5] but the case presented here is the first to our knowledge describing the phenomenon of palmoplantar squamous cell carcinomas in a patient from this region. Determining the cause of her lesions, however, is difficult, because there is a 20-to-30-year latency period between the onset of exposure and development of characteristic keratosis, [10] and metrics for estimating past arsenic exposure are imperfect. Biologic monitoring with urine, blood, hair, and nail samples may help assess recent and/or ongoing exposure yet is less accurate in determining past levels [10, 15]. Work from Chile did show elevated arsenic in hair six years after mitigation, [16] although this picture is complicated by the possible external deposition of arsenic on hair shafts. Calculation of the average daily or cumulative arsenic consumption using known arsenic concentrations in drinking water is another option to assess exposure but may be limited in regions where these values are unknown or vary widely and in patients who drink water from multiple sources or have variable consumption habits [10,15]. Ultimately, while estimating magnitude of exposure is important for risk stratification, it is most imperative that

dermatologists be aware of the public health burdens of chronic arsenic exposure and vigilant in monitoring patients who have spent substantial time in high-risk regions internationally and domestically.

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