

A Case of Arsenical Keratoses After Chronic Consumption of Water from Tube Wells

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Disclosures: None

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Abstract

Arsenic has been shown to increase the risk of developing skin cancers, including basal cell carcinoma and squamous cell carcinoma. A 44-year-old male from Bangladesh presented to the clinic for evaluation and treatment of scaly plaques on his palms and soles, and skin biopsy showed arsenical keratosis. The World Health Organization defines the maximum amount of arsenic allowed in drinking water as 0.01 mg/L, but testing of tube wells in Bangladesh found that up to 30% had levels exceeding 0.05 mg/L. This represents approximately 36 million people at risk of drinking water with unsafe levels of arsenic. This case highlights the importance of being aware of this rare presentation, as early treatment and close monitoring is key to preventing cutaneous malignancies.

Case Report

A 44-year-old male presented to the clinic for evaluation and treatment of scaly plaques on his palms and soles. On physical exam, there were diffuse, punctate, hyperkeratotic, yellow-to-brown plaques on both palms (**Figure 1**) and large, hyperkeratotic, scaly plaques on the soles of both feet (**Figure 2**). The patient had been using multiple emollients, including urea, ammonium lactate, and salicylic acid, with minimal effect.

The patient was a native of Bangladesh until 2009, when he moved to the United States. During most of his life, he drank water from tube wells, which were the only available sources of water in his town. His lesions started developing approximately 15 years prior as small, scaly plaques. Initially, the areas were itchy, but they had been asymptomatic for several years. His past medical history was significant for diabetes mellitus and hyperlipidemia. His surgical history was significant for cholecystectomy. Labs were obtained, which showed elevated triglycerides, LDL and VLDL as well as elevated glucose levels. All other labs were within normal limits. A shave skin biopsy was obtained from one of the plaques on the patient's right hand, and histopathology showed papillated and acanthotic epidermis with some hints of keratinocyte atypia and overlying columns of hyperkeratotic parakeratosis alternating with hyperkeratotic orthokeratosis (**Figures 3, 4**). The clinical/pathological correlation was consistent with arsenical keratoses.

Our patient did not have any symptoms, and he decided to use topical modalities to reduce the hyperkeratosis and overall appearance. The patient was treated with topical 5-FU under occlusion and daily emollients, which provided significant symptom relief. No cutaneous malignancy was found on initial exam or on follow-up. Although a cutaneous malignancy was not appreciated, periodic check-up was instructed, as chronic exposure to arsenic has been shown to be a risk factor for skin malignancies.⁶

Discussion

The contamination of water with arsenic in Bangladesh has been called the "largest poisoning of a population in history."² By the 1990s, up to 95% of Bangladesh's population was drinking from tube wells. The World Health Organization (WHO) defines the maximum amount of arsenic allowed in drinking water as 0.01 mg/L; however, testing

in Bangladesh showed that up to 30% of tube wells had levels exceeding 0.05 mg/L, representing approximately 36 million people drinking water with unsafe levels of arsenic.² Trivalent inorganic arsenic is the most toxic form, with a latent period of up to 50 years; therefore, symptoms of chronic exposure to arsenic can show up later in life. Furthermore, arsenic is considered a class I human carcinogen by the International Agency for Research on Cancer, mostly because of the increased risk for cancer in organs such as the lung and bladder.¹ In a recent study, the Health Effects of Arsenic Longitudinal Study (HEALS), there was an increase in overall mortality rate among people exposed to arsenic compared to control cohorts. The study concluded that in the studied population, an estimated 21.4% of all deaths and 23.5% of deaths associated with chronic disease could be attributed to arsenic exposure. An important finding in this longitudinal study was the associated increase in overall mortality in people chronically exposed to arsenic at relatively low concentrations compared to prior studies.¹⁵ This highlights the risk to our patient, since he was exposed to arsenic through drinking water over a long period of time.



Figure 1. Small, punctate, yellow hyperkeratotic plaque on palm.



Figure 2. Multiple brown-yellow hyperkeratotic plaques on sole.

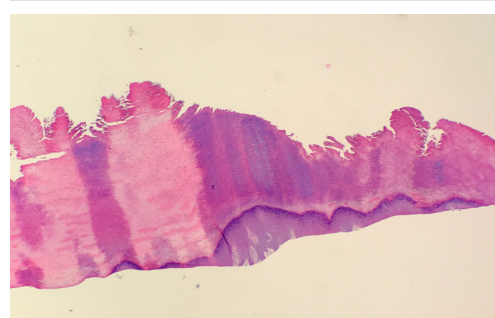


Figure 3 (4x). Papillated and acanthotic epidermis with overlying columns of hyperkeratotic parakeratosis alternating with hyperkeratotic orthokeratosis.

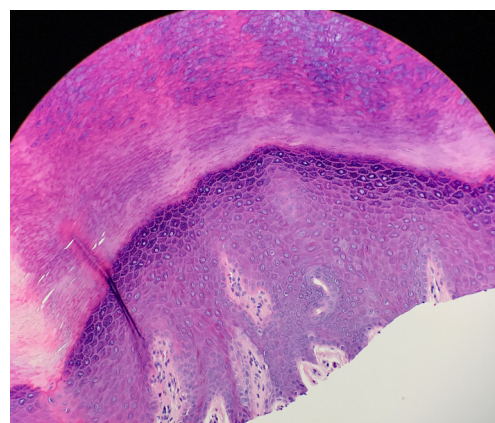


Figure 4 (20x). Hints of keratinocyte atypia within the superficial portion of the spinous and granular layers.

Background

Atomic number 33, also known as arsenic, was discovered by Albertus Magnus in 1250.¹ It was later that German physician and pharmacologist Johann Schroder recognized arsenic as an element. Arsenic occurs in the environment and can combine with other elements to create inorganic arsenic compounds. Arsenic changes its form in the environment by reacting with oxygen and other molecules in the air, water or soil. This element has the capacity to attach itself to large- or small-capacity molecules that can settle in soil.¹ Its fluidity enables it to be present in lakes, rivers, and underground water. Around the globe, initiatives to prevent geographical arsenic contamination have been undertaken, including testing drinking water, heavily regulating pesticides and industrial compounds, and implementing organic farming. Despite 21st century interventions, arsenic continues to contaminate the drinking supply in some developing countries.² Regions most impacted by pollution from naturally occurring arsenic in groundwater are Central America, Africa, and South and Southeast Asia.^{3,4}

Pathogenesis

The pathogenesis of arsenic's toxicity to humans is thought to be an interference with cellular respiration and uncoupling of oxidative phosphorylation. Arsenic can also cause direct effects to DNA in areas of transcription, repair and amplification. Furthermore, tumor-suppression factors such as p53, nuclear factor-kappaB and activating protein-1 have been affected by arsenic exposure. A study in the *Journal of Cutaneous Pathology* also demonstrated that arsenic exposure induces abnormal keratinocyte differentiation via the effects of integrin expression.⁵ Arsenic causes oxidative stress through the production of reactive oxygen species and reactive nitrogen species.⁶ A recent article in *Cancer Letters* provides a detailed explanation of the pathway by which arsenic induces oxidative stress. Arsenic increases expression and activity of NADPH oxidase by upregulation of the protein p22hox and by the translocation of Rac1 (a low-molecular-weight guanosine triphosphate), which is responsible for the activation of NADPHO. Nitric oxide (NO), a molecule involved in multiple protective roles such as vasodilation and anti-inflammation, is downregulated by arsenic through inactivation of NO synthase.⁶ Exposure to arsenic has been shown to carry an increased risk for development of skin cancers including basal cell carcinoma and squamous cell carcinoma.

Cutaneous and Systemic Disease

Arsenic exposure can lead to a broad spectrum of cutaneous findings, including hyperpigmentation, hyperkeratosis of the palms and soles, Bowen's disease, squamous cell carcinoma, and basal cell carcinoma. One of the earliest findings of arsenic exposure is changes in pigment, especially on the palms and soles. These changes are described as macules, leukomelanosis, and mucosal pigmentation. Ruiz et al. graded the progression of skin findings on a scale from mild to severe, mostly defined by lesion size, from less than 2 mm (mildest) to greater than 5 mm (most severe).⁷ Severe disease can include fissuring and cracking of the skin. More than 40% of affected people develop keratosis of the palms and soles. The lesions are hyperkeratotic, and they can be erythrodermic. The keratoses can be very exophytic and cause discomfort when walking or under direct pressure. They favor the thenar and hypothenar eminences, distal palms, lateral fingers, dorsal aspect

of IP joints, and weight-bearing plantar surfaces. Although rare, there are reports of arsenical keratoses on the trunk, proximal extremities, eyelids and both male and female genitalia.⁸

Systemic effects of arsenic toxicity can be categorized as either acute or chronic. Acute effects include flushing of skin, erythema, alopecia, Mees' lines, abdominal pain, diarrhea, pancytopenia, cardiac arrhythmias, renal failure, respiratory failure, and acute neuropathy that can progress to Guillain-Barre-like ascending paralysis. Chronic exposure is often summarized by skin abnormalities, hyperpigmentation and keratoses; other systemic effects of chronic arsenic exposure include nasal-septum perforation, peripheral neuropathy, bone-marrow hypoplasia, chronic diarrhea, obstructive or restrictive lung disease, diabetes mellitus, and hepatomegaly that can lead to hepatic fibrosis.⁹

Malignancies

Cutaneous malignancies include basal cell carcinoma, squamous cell carcinoma and, less often, Merkel cell carcinoma. These non-melanoma skin cancers occur on non-sun-exposed areas and tend to be multiple. Invasive squamous cell carcinomas arising from keratoses in arsenic-exposed areas are more likely to metastasize than those arising from normal skin. Other reported non-cutaneous malignancies include genitourinary cancers, especially of the bladder, as well as lung and liver cancers.⁹

Histopathology

Arsenical keratosis has prominent hyperkeratosis and papillomatosis without atypia. There is a moderate amount of parakeratosis and vacuolation of keratinocytes. Adnexal structures are spared. There are variable changes of dermal connective tissue. When malignancy is present, the features are the same as in cases not related to arsenical toxicity.¹⁰

Differential Diagnosis

Arsenical keratosis bears a close resemblance to palmoplantar psoriasis, palmoplantar keratoderma and verruca vulgaris. The inherited keratodermas are differentiated by central keratotic plugs in small pits; arsenical keratoses do not have plugs. Psoriasis has more scale and involvement of other body areas. In the nevoid basal cell carcinoma syndrome, onset is early, and there are other characteristic features, including odontogenic jaw cysts and typical basaloid proliferative histology.⁹

Treatment

The pillar in management of arsenical keratosis is recognition, as lesions may develop into cutaneous malignancies, and chronic exposure can lead to visceral malignancies. There are multiple treatment options, and effectiveness appears to vary case by case. Choice of treatment modality needs to consider the chronicity of arsenic exposure as well as patient tolerance of therapy options. In acute arsenic toxicity, the mainstay is chelation therapy with a 3 mg/kg intramuscular injection of dimercaprol or British antilewisite (BAL) every four hours for two days, then every six hours for one day, and then every 12 hours for 10 days.¹⁰ For cutaneous lesions, therapy modalities have included cryotherapy, topical chemotherapy, photodynamic therapy and retinoids. Retinoids have long been studied. They have been shown to change the terminal differentiation of cells to non-keratinizing epithelium. Yerebakam et al. found 1 mg/kg of acitretin daily for 10 months resulted

in improvement of arsenical keratosis lesions.⁸ Although a few reports note vast improvement of lesions with management via oral acitretin, solo therapy has been found to be ineffective in other cases. Topical 5-fluorouracil is a mainstay topical chemotherapeutic agent used in the treatment of actinic keratosis and Bowen's Disease.¹² Intralesional 5-FU has been used as a treatment modality in some patients with basal cell carcinoma and squamous cell carcinoma. In the case of arsenical keratosis, a combination of acitretin and intralesional 5-FU has been tried. Combining keratolytics and acitretin has proven effective in limited cases. An alternative therapy is imiquimod, an immune-response modifier causing activation of immune cells to produce cytokines. Lonergan et al. reported success with imiquimod cream 5% topical daily for six weeks, with no evidence of recurrence of arsenical cutaneous lesions after more than three years.¹³ Clinicians also report success with the use of photodynamic therapy. Herbert et al. reports one case of refractory arsenical keratosis managed with photodynamic therapy using visible blue light and topical 20% weight/volume aminolevulinic acid (ALA).¹⁴ There is still room for investigation regarding photodynamic therapy as well as the possible synergetic efficacy of various topical chemotherapeutic and keratolytic agents.

References

1. Agency for Toxic Substances and Disease Registry [Internet]. [Accessed 24 Jan. 2018]. Available from: <http://www.atsdr.cdc.gov>.
2. The World Health Organization. Guidelines for Drinking Water Quality. 3rd ed. Geneva; 2008. 668 p.
3. Garelick H, Jones H, Dybowska A, Valsami-Jones E. Arsenic pollution sources. Rev Environ Contam Toxicol. 2008;197:17-60.
4. Kumar A, Kumar P, Rahman S, Iqbal A, Ali M, Niraj PK, Anand G, Abhinav, Ghosh AK. Ground Water Arsenic Contamination: a local survey in India. Int J Prev Med. 2016 Aug 9;7(1):100.
5. Lee CH, Chen JS, Sun YL, Liao WT, Zheng YW, Chai CZ, Chen GS, Yu HS. Defective β_1 -integrins expression in arsenical keratosis and arsenic-treated cultured human keratinocytes. J Cutan Pathol. 2006 Feb;33(2):129-38.
6. Hunt KM, Srivastava RK, Elmets CA, Athar M. The mechanistic basis of arsenicosis: pathogenesis of skin cancer. Cancer Letters. 2014 Nov 28;354(2):211-9.
7. Ruiz de Luzuriaga AM, Ahsan H, Shea CR. Arsenical Keratoses in Bangladesh-update and prevention strategies. Dermatol Clin. 2011 Jan;29(1):45-51.
8. Wong SS, Tan KC, Goh CL. Cutaneous Manifestations of Chronic Arsenicism: review of seventeen cases. J Am Acad Dermatol. 1998 Feb;38(2):179-85.
9. Bologna JL, Lorizzo JL, Schaffer JV. Dermatology. 3rd rev. ed. London: Saunders; 2012. 2776 p.
10. Patterson JW. Weedon's skin pathology. 4th ed. Hosler GA, contributor. London: Churchill Livingstone; 2016. 1262 p.
11. Hoffman RS, Howland MA, Lewin NA, Nelson LS, Goldfrank LR. Goldfrank's Toxicological Emergencies. 10th ed, New York: McGraw Hill Education; 2015. 1904 p.
12. Habif TP. Clinical Dermatology: a color guide to diagnosis and therapy. 6th ed. Amsterdam: Elsevier; 2015. 1064 p.
13. Lonergan CL, McNamara EK, Cordoro KM, Greer KE. Imiquimod cream 5% for the treatment of arsenic-induced cutaneous neoplasms. Cutis. 2010 Apr;85(4):199-202.
14. Adelaide H, Phillips C, Hymes S, Wang W. Photodynamic therapy for arsenical keratoses. J Am Acad of Dermatol. 2010 Mar 1;62(3 Sup 1):AB115-AB115.
15. Ahsan H, Chen Y, Parvez F, Hussain AI, Argos M, Momotaj H, Levy D, van Geen A, Howe G, Graziano J. Health Effects of Arsenic Longitudinal Study (HEALS): description of a multidisciplinary epidemiologic investigation. J Expo Sci Environ Epidemiol. 2006 Mar;16(2):191-205.