Speckled Pigmentation and Palmoplantar Keratoses Leading to the Mass Detection of Chronic Arsenic Poisoning

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ABSTRACT

Arsenic is a known human carcinogen and skin manifestations are the earliest and most specific markers of chronic arsenic poisoning. A 43-year-old man from Luzon presented at the Section of Dermatology with a one-year history of hyperkeratotic papules and plaques on the palms and soles. Numerous round hypopigmented macules were scattered on the upper back. Initial 24-hour urine arsenic level was elevated at 288mcg/liter. The patient underwent successful chelation with N-acetylpenicillamine and the palmoplantar keratoses were treated with cryotherapy and topical 20% salicylic acid in white petrolatum. In cooperation with the Department of Health, a comprehensive health and environmental assessment was conducted in the affected communities. This case highlights the role of dermatologists in the diagnosis and management of this public health problem.

Key Words: arsenic poisoning, Philippines, palmoplantar keratoderma, hyperkeratotic papules, chelation

Introduction

Chronic arsenic poisoning is defined by the WHO as "a chronic health condition due to prolonged ingestion of arsenic above a safe dose for at least 6 months, usually manifested by characteristic skin lesions of melanosis and keratosis, occurring alone or in combination, with or without involvement of internal organs."[1]

Arsenical keratoses are 2-5 mm punctate papules most commonly found on the palms and soles but can also occur in the trunk.[2] Pigmentary changes secondary to arsenic can appear as fine-freckled or the "rain-drop in dusty road" pattern, as localized pigmentation, as diffuse pigmentation, and as pigmentation around the mucosa.[1]

In a review of epidemiological studies on chronic health effects of arsenic by Yoshida, Yamauchi, and Sun, pigmentary changes and arsenical keratoses are the earliest and most specific signs of chronic arsenic keratoses; both are seen in patients taking in an arsenic contaminated water with concentration as low as 0.05 mg/L.[3]

Arsenic is a human carcinogen and is associated with complications such as obstructive and interstitial lung disease, pulmonary carcinoma, portal hypertension and liver cirrhosis, diabetes, stillbirths and abortions in pregnant women ingesting arsenic above safe levels, anemia leukopenia and thrombocytopenia, ischemic heart disease, dyspepsia, renal failure, and cancer of the kidneys and urinary bladder.[4,5]

Clinical Case

A 43-year-old man from Luzon came in for one-year history of multiple papules and plaques with hyperkeratotic surface on the palms and soles. The persistence and increase in number of the lesions caused him to avoid social interactions due to embarrassment thus prompting medical consult at the outpatient clinic of the Section of Dermatology of the Philippine General Hospital on July 2014. No other family members were found to have the same symptoms but patient alleged that he has seen locals with similar lesions on the palms and soles. Upon probing, the patient reported of a paper mill factory in the municipality that has been operational before onset of the lesions. His diet consisted of locally sourced meat, seafood and vegetables. Water for drinking and cooking came from the local municipal water district pipeline.

Systemic physical examination was essentially normal and neurologic examination revealed no gross motor and sensory deficits. There were multiple yellow discrete papules and plaques with hyperkeratotic surface on the palms and soles (Figures 1 and 2). There were no alopecic patches, no pigmentation of the mucosa, and no nail changes. On the patient's trunk were numerous round hypopigmented macules scattered within hyperpigmented patches, giving an overall appearance akin to "raindrops on a dusty road" (Figure 3).

Punch biopsy of a hyperkeratotic papule on the palm showed dyskeratotic and atypical cells within the epidermis that are consistent with arsenical keratosis. Pre-treatment 24-hour urine arsenic level was elevated at 288 microgram/liter.

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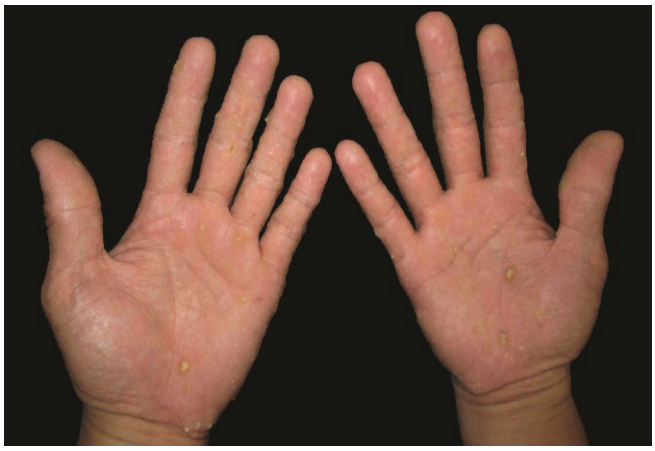

Figure 1. Punctate papules with hyperkeratotic surface on the palms.

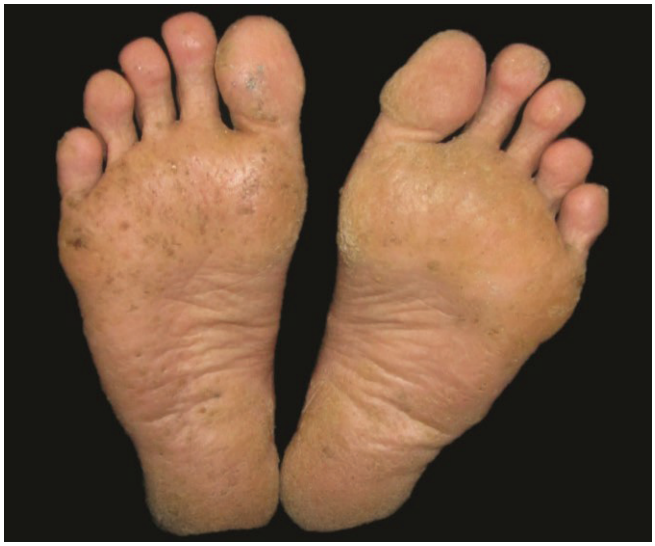

Figure 2. Hyperkeratotic plaques on the bilateral soles.

Figure 3. Speckled pigmentation on the skin on the patient's back resembling "raindrops on a dusty road."

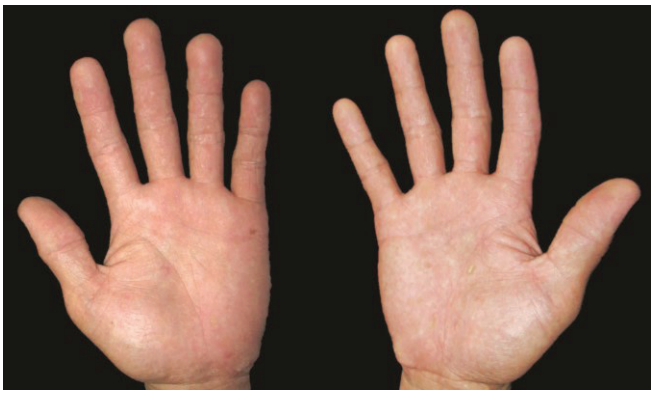

Figure 4. Decreased thickness of hyperkeratotic plaques on the palms after 6 weeks of nightly application of topical 20% salicyclic acid in white petrolatum.

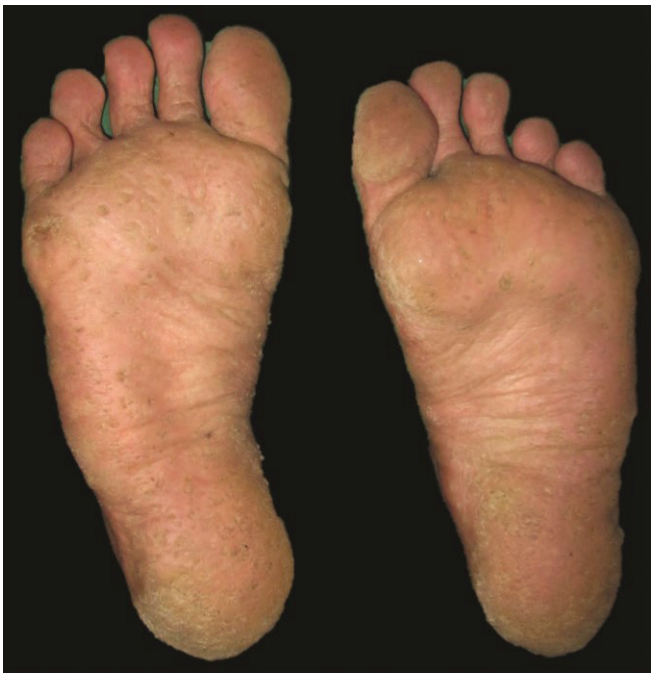

Figure 5. Decreased thickness of hyperkeratotic plaques on the soles after 6 weeks of nightly application of topical 20% salicyclic acid in white petrolatum.

The patient was co-managed with the unit of Toxicology of our institution for further work-up and chelation. Laboratory work-up and imaging studies were normal except for elevated serum creatinine at 157 micromole/liter with a computed creatinine clearance of 53.10 mL/minute using the Cockcroft-Gault formula. Chelation was done as an in-patient procedure and 15 doses of oral N-acetylpenicillamine, at 250 mg per dose, were given every 8 hours. No untoward events were noted during the administration of N-acetylpenicillamine. While on chelation, dietary iron and milk restriction, vitamin C supplementation, and consumption of arsenic-free commercially bottled water was strictly observed. After completing 15 doses of N-

acetylpenicillamine, urine arsenic level decreased to the upper normal limit of 50 microgram/liter. After chelation, serum creatinine level had decreased to 135 micromole/liter, a computed creatinine clearance of 61.75 milliliter/minute, and normal serum electrolytes.

Symptomatic treatment of palmoplantar keratoses was done with one session of cryotherapy and daily topical application of 20% salicylic acid in white petrolatum under occlusion. After 6 weeks of topical salicylic acid ointment, there was marked decrease in the thickness and number of the arsenical keratoses (Figures 4 and 5). Patient reported mild and transient pruritus upon application with no burning sensation and no erythema.

Discussion

The impact and burden of arsenic poisoning, especially in vulnerable developing countries where anthropogenic and natural causes are prevalent, is staggering as an estimated 30-60 million people in the South East Asian region are exposed to arsenic.[6]

The International Agency for Research on Cancer categorizes arsenic as a class 1 carcinogen to humans based on the review of studies that have shown dose-response relationship between the level of arsenic found in the water and the risk of developing cancer. In particular, cancers of the skin, lungs, liver, kidneys and prostate were among those found to have causal relationship with increased arsenic exposure.[7] Malignancies may appear decades after exposure and even with cessation of exposure.[1,8] Therefore treatment and long-term monitoring is part of the management plan of all cases of chronic arsenic poisoning.

The treatment of our patient included cessation of exposure, enhanced excretion of arsenic and symptomatic treatment of skin lesions. Chelating agents such as oral N-acetylpenicillamine forms a chelate structure with arsenic thus enhancing renal excretion. Our patient was given N-acetylpenicillamine at a dose of 10mg/kg/day as recommended by the treatment guidelines of the National Poison Management and Control Center (NPMCC).[9] Supplementation with dietary proteins and antioxidants such as vitamin C are said to oppose the deleterious generation of reactive oxygen species by arsenic thru scavenging of free radicals.[10,11]

Cryotherapy is an accepted surgical procedure to remove arsenical keratoses.[12] After debulking with cryotherapy, the patient was asked to apply topical 20% salicylic acid in white petrolatum nightly to improve the appearance. This concentration of salicylic acid is above the recommended 5-10% by the WHO but has been shown in a randomized controlled trial to produce faster results with few reported adverse events such as burning and pruritus.[13] With just 6 weeks of application, the patient was immensely satisfied with the outcome as there was noticeable improvement in the palmoplantar keratoderma. The regimen was also acceptable to the patient as it was easy to follow and he reported only occasionally itching.

Laboratory determination of arsenic concentration in biological and non-biological samples requires time and funds. However, treatment should already be initiated while waiting for the results as the dermatologic signs of pigmentary changes and keratoses are specific and correlate with arsenic exposure.

The WHO, in its field guide for arsenic poisoning detection, management and surveillance, emphasized the role of a trained dermatologist or arsenic expert in clinically confirming cases and ruling out the differentials thru in-depth skin examination.[1] Some acquired dermatoses can mimic arsenical keratosis. Verruca vulgaris can present anywhere in the body as hyperkeratotic papules and plaques. Histologically, koilocytes are seen in verruca vulgaris but are not found in arsenical keratoses. Keratoses from corns, calluses and occupational exposure are distributed along areas of friction. In contrast, arsenical keratoses can affect the whole palms and soles.[1]

In dark skinned individuals, the lesions of pityriasis versicolor can mimic the fine- freckled or spotted pigmentation of chronic arsenic poisoning. Pityriasis versicolor is a superficial fungal infection caused by *Malassezia furfur* that usually presents as hypopigmented or hyperpigmented macules and patches distributed over the back and shoulders.[12] However, in pityriasis versicolor there usually is fine scaling, which is not seen in chronic arsenic poisoning.

Arsenic poisoning is a public health threat and as physicians we must fulfill our role as health leaders and patient advocates. We reported this case to the Department of Health and the NPMCC because we wanted to investigate the burden of this disease and to extend our services and expertise in the management of such cases. Cooperation with concerned government agencies in two comprehensive health and environmental assessment missions led to mass detection of chronic arsenic poisoning. Results from the environmental assessment indicated a geogenic source of arsenic that contaminated the ground water. The paper mill, which was located downstream from the water source, has been subsequently cleared.

Documented cases of arsenic poisoning in Philippines are found in Davao City[14,15] Batangas province,[16] Marinduque province,[17] and near the Mt. Apo Geothermal powerplant.[17] Our patient is the first registered case of chronic arsenic poisoning from the patient's province in Luzon. According to the Disease Prevention and Control Bureau of the DOH, no national database on arsenic poisoning exists. Thus, the authors recommend mandatory reporting of suspected and confirmed arsenic poisoning cases to concerned health agencies to improve the health reporting system and to aid the agencies in investigating arsenic poisoning. We have seen the positive outcomes of

interagency cooperation in the benefitting of the public. The local government unit provided alternative sources of drinking water and closure of pumping stations that were believed to be contaminated. Affected members of the community were sent to a tertiary hospital for monitoring and chelation. Public health lectures and continuing medical education intended for municipal health officers were conducted by board-certified dermatologists. In 2015, an Inter-Agency Task Force on Arsenic Risk Management was created by then-president Benigno Aquino III to address the needs of the community affected by arsenic poisoning.[18]

Statement of Authorship

All authors have approved the final version submitted.

Author Disclosure

All the authors declared no conflicts of interest.

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