Squamous cell carcinoma secondary to arsenic keratoses in a father and son

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Arsenic is categorized as a class I human carcinogen by the International Agency for Research on Cancer and chronic exposure to its inorganic form have been associated with a variety of diseases. Its effect on the skin is the most sensitive endpoint of arsenic exposure and dermal manifestations include arsenic keratoses, a premalignant lesion and considered a diagnostic criterion of arsenic toxicity. We report two cases of chronic arsenic poisoning in a father and son who presented with a history of hypo- and hyperpigmented macules and patches over the body and multiple hyperkeratotic papules over the palms and soles, progressing to ulceration. All other family members, except for one, also had the pigmentary changes on the body and palmoplantar hyperkeratosis. Histopathology results of the ulcerated lesions of both patients were consistent with squamous cell carcinoma. Surgical interventions, oral retinoids, and nutritional buildup were done. The patients are being followed up every six months to monitor cancer progression and internal organ involvement. These cases highlight the role of occupational and environmental exposure to arsenic as an important risk factor in developing keratoses and cancer.

Keywords: arsenic, arsenic keratoses, squamous cell carcinoma

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INTRODUCTION

Arsenecosis is a condition arising from prolonged exposure of arsenic above safe levels for at least six months, usually manifested by characteristic skin lesions of melanosis and keratosis, occurring alone or in combination, with or without the involvement of internal organs.[1] Millions of people worldwide are exposed to toxic levels of arsenic coming from industrial, agricultural, and medical substances; contamination of drinking water poses the greatest threat to health.[2] Reported countries include: Bangladesh, Mongolia, Taiwan, Mexico, USA, and Northern/ Eastern Europe.[3] In the Philippines, particularly North Cotabato published reports on arsenic exposure from geothermal power plant, 39 residents had skin lesions consistent with arsenic keratoses.[4] In 2002, another report from Sta. Cruz, Davao del Sur revealed a case of arsenic keratoses and squamous cell carcinoma.[5] In 2016, there have been 123 reported arsenicosis cases in the Central Luzon Region.[6]

Chronic exposure to inorganic arsenic, which is categorized as a class I carcinogen by the International Agency for Research on Cancer, is associated with skin, lung, bladder, kidney, and liver cancers.[7] The skin is the most sensitive endpoint of exposure as arsenic tends to concentrate in ectodermal tissue (e.g., skin, hair, and nails).[8] Dermal manifestations of chronic exposure include punctate, yellowish, hyperkeratotic papules known as arsenic keratoses, and finely freckled symmetrical hyperpigmentation and hypopigmentation on the trunk and extremities.[9] Arsenic keratoses occur at sites of trauma, especially on the palms and soles. These are premalignant lesions and considered a diagnostic criterion of arsenic toxicity.[2]

Arsenic-related skin cancers develop either de novo or from Bowen's disease and has a latency period of 10 to 30 years.[2,10] According to Chen et al., 55% of squamous cell carcinoma arise from pre-existing arsenic keratoses or Bowen's disease.[11]

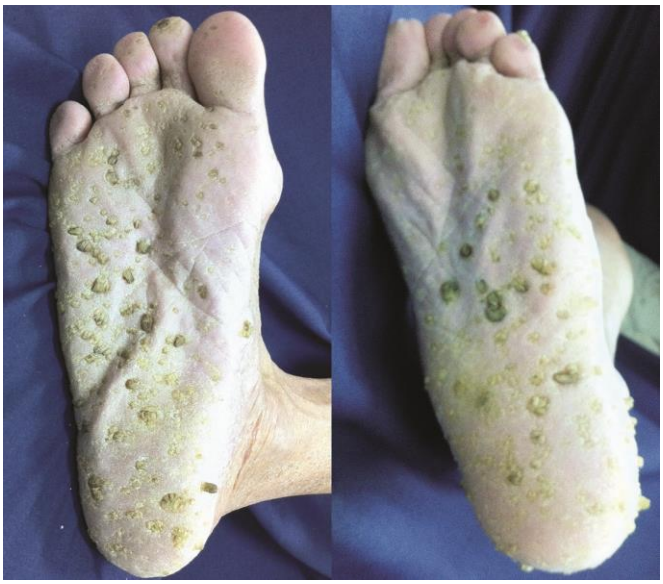
CASE REPORT

We present a 60-year-old father and his 29-year-old son, both farmers from Compostela Valley, who consulted for an ulcerated wound on the right palm, and an exophytic mass with ulceration and necrosis on the right index finger, respectively. In their family of six, only the third son had no similar lesion. The wife (died at age 48 of cancer), eldest son (died at age 48 of cancer), and second son (died at age 45 of liver disease) have presented with hyperkeratotic lesions on the palms and soles.

The case of the father spanned 27 years. Initially, he presented with multiple hypopigmented and hyperpigmented macules on the trunk; and pruritic, hyperkeratotic papules on the palms and soles. Over the years, the papules on the right palm ulcerated and easily bled with minimal trauma; Five months prior to consult, he noted inability to flex and extend the digits of his right hand.

The son presented with the same lesions as the father over a span of 20 years. Two years prior to consult, the

papules on the right index finger ulcerated and easily bled with minimal manipulation. A year later, a mass grew on the



right index finger with ulceration and foul-smelling discharge was noted.

The father worked in a cornfield from 1973 to 1985 and in a banana plantation from1985 to 1990 situated near their home. The son started to work in the same banana plantation at age 10 from 1992 to 1995. Both worked in their family

owned land after. Their family previously used groundwater from a dug well as their water supply for more than 10 years and bought from water refilling stations thereafter.

On physical examination, the father had multiple hypo- and hyper-pigmented macules and patches over the entire body excluding face; multiple, punctate, hyperkeratotic papules on the palms and soles (Figures 1 and 3a); and ulcerated stellate shaped 2.5x2cm wound with thickened borders and contracture on the right palm (Figure 3a).

The son had a firm, non-moveable mass measuring 3x4cm over the right upper arm. There were multiple hypopigmented and hyperpigmented macules and patches over the entire body; multiple punctate, hyperkeratotic papules on the palms and soles, and a nodule measuring 2x2cm over the plantar surface of the right foot (Figure 2); an exophytic mass with ulceration and necrosis on the right index finger (Figure 3b).

Several diagnostic tests were done including CBC, serum

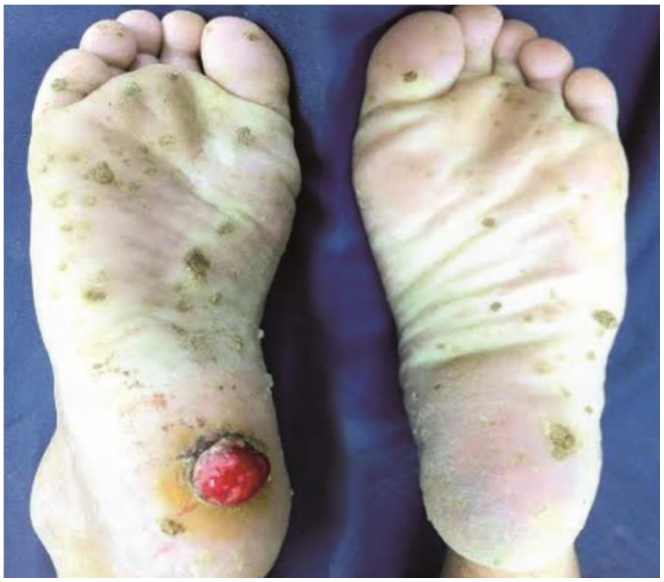
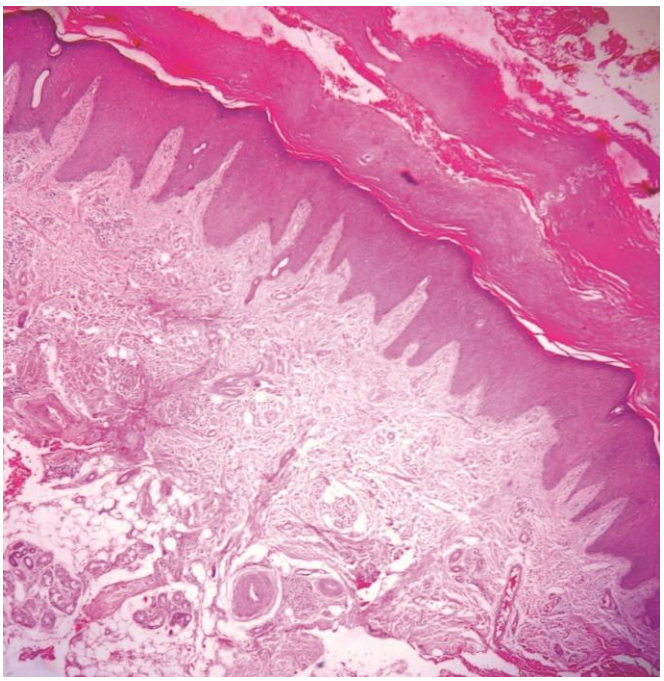


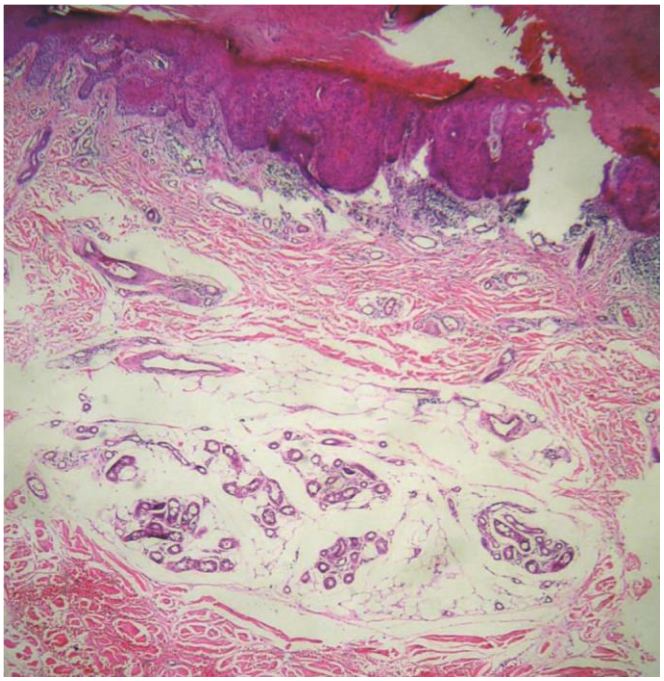
Figure 1. Soles of the feet (Father) showing multiple punctate and hyperkeratotic papules.

electrolytes, blood chemistry, chest X-ray, CT scan, AFB sputum smear, USD of whole abdomen, liver enzymes, Doppler USD of extremities, skin, tissue and core needle biopsy, blood, urine and hair arsenic levels. (Table 1). Water samples from the groundwater wells that both patients used as water supply until 2002 showed elevated arsenic levels of 960µg/L and 1,650µg/L. All samples for arsenic level determination were sent last July 2012 to Chempro Analytical Services Laboratories in Pasig City, one of the FDA accredited laboratories in the Philippines.

The father was treated for tuberculosis while the son was treated for pneumonia. The father underwent below-elbow amputation of the right arm, while his son underwent ray amputation of the right index finger. For the son, surgical intervention is contemplated on the squamous cell carcinomas located on the right upper arm and right foot. Oral retinoids and nutritional build up, including multivitamins with folic acid, were initiated. Follow-up every six months was advised.

Figure 2. Soles of the feet (Son) showing punctate and hyperkeratotic papules. Right sole shows 2x2cm nodule over the plantar surface.





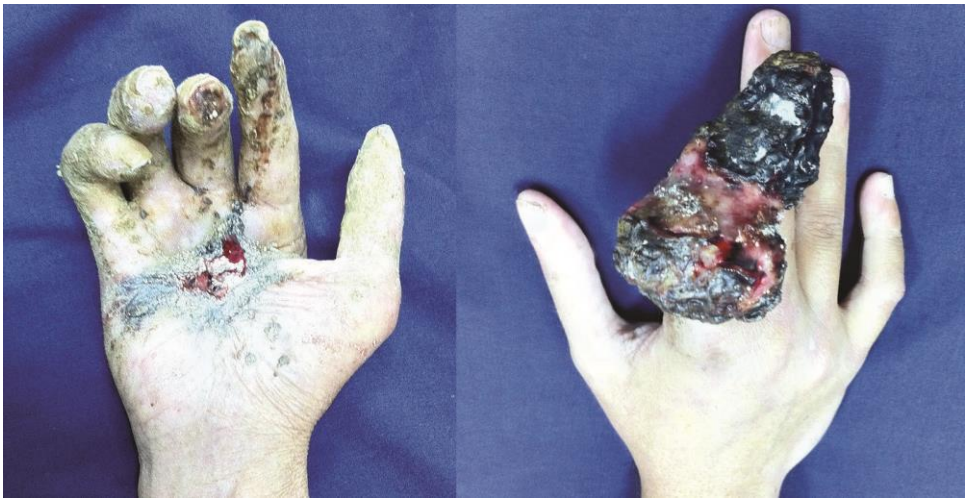


Figure 3a. Ulcerated wound and contracture, right palm (Father); **Figure 3b.** Exophytic mass with ulceration and necrosis, right index finger (Son) **Figure 4a.** Hyperkeratosis, Hypergranulosis, Irregular Acanthosis with **Figure 4b.** Hyperkeratosis, Irregular Acanthosis with disorganized epidermal disorganized epidermal cells, Dilated capillaries with hemorrhages, cells, Lichenoid infiltrates composed of lymphocytes and histiocytes perivascular and interstitial infiltrates composed of lymphocytes, histiocytes, eosinophils with extravasated RBCs

Table 1. Diagnostic Results for both patients

DIAGNOSTICS	FATHER	SON
CBC	Eosinophilia	Leukocytosis with neutrophilic predominance
Serum Electrolytes	Hyponatremia, Hypokalemia	
Blood Chemistry	Normal	
CXR	Consolidative Pneumonia vs Pulmonary Nodule on right mid lung field	Left Basal Pneumonia
CT-Scan*	Bilateral cavitary pulmonary tubeculosis	—
Acid Fast Bacilli Sputum Smear	Positive	—

Ultrasound of Whole Abdomen	Coarsened Parenchymal disease, to consider liver parenchymal disease	Normal
Liver Enzymes	Normal	—
Doppler Ultrasound **	Right upper extremity: unremarkable arterial and venous studies	—
Skin Punch Biopsy	Papule over palm: Figure 4a Squamous Cell Carcinoma In Situ	Papule over palm: Figure 4b Squamous Cell Carcinoma In Situ
Tissue Biopsy	From below elbow amputation of right arm: Squamous Cell Carcinoma, Well Differentiated type	Nodule over plantar aspect, Right foot: Squamous Cell Carcinoma
Core Needle Biopsy	—	Mass on R arm: Squamous Cell Carcinoma
Blood Arsenic Level	Elevated	
Urine and Hair Arsenic Level	Normal	
Nail Arsenic Level	Inadequate sample for testing	

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DISCUSSION

Our patients presented with leukomelanosis and hyperkatotic changes, elevated blood arsenic levels, normal urine and normal hair arsenic levels. Water samples obtained from the ground water wells patients used for consumption showed elevated arsenic levels. The World Health Organization defined arsenicosis as the presence of pigmentary and keratotic skin lesions, and evidence of exposure to elevated levels of arsenic.[1] With the skin lesions and history of intake of arsenic contaminated water, our patients fulfilled two major criteria of arsenicosis, validating the diagnoses of Arsenic Keratoses.

Arsenic keratoses was the primary consideration due to the patients' clinical presentation, the sequential appearance of the lesions and the probable exposure to arsenic from the groundwater. Skin manifestation is characterized by the development of spotted pigmentation followed by the gradual appearance of hyperkeratotic changes. Arsenic keratoses may be precursor of malignancy after a long latency period.[1,11] These were evident in both patients. The most common type of malignancy following chronic arsenic exposure are squamous cell carcinoma in situ, squamous cell carcinomas or basal cell carcinomas.[1] Clinical presentation of erythematous cruted nodules and exophytic mass favor SCCIS and SCC. Histopathologic findings further reinforced the diagnosis of arsenic keratoses, squamous cell carcinoma in situ, and squamous cell carcinoma. Hematologic manifestations associated with arsenic keratoses include

leukopenia and relative eosinophilia.[1,11] The father had eosinophilia but the son had leukocytosis probably because of the concomitant pneumonia at the time of examination.

Arsenic-induced squamous cell carcinoma pathogenesis involves dysfunctional keratinization, which promotes the formation of DNA crosslinks, thus, impairs DNA replication.[12] The high affinity of arsenic to sulfhydryl groups in keratinrich cells contributes to its accumulation in epithelial cells and stimulates malignant transformation.[13] When arsenic enters the body, it undergoes biotransformation and generates reactive oxygen species (ROS) induced DNA damage.[2] Generation of ROS has been described as one of the earliest and most important mechanisms of arsenic-induced carcinogenicity.[14]

Arsenic toxicity results from absorption of its inorganic compounds. Inorganic arsenic compounds are rapidly cleared from the blood via the kidneys and eliminated by the urine, thus, blood and urine levels have been previously used to reflect recent exposure.[15] However, a study identified that in chronic exposure, steady state concentration in the blood is achieved and suggested that blood may be a marker for past exposure, this statement however needs to be further validated.[16] Our patients presented with normal urine arsenic levels with elevated serum arsenic levels prompting more of chronic past exposure than a recent contact.

Arsenic has high affinity for the sulfhydryl groups in keratin, making the hair and nails good measures of past exposure.[14] However, arsenic does not remain in these tissues for long, by the time neoplasms have developed the concentrations of arsenic in the hair and nails may return to normal. It has also been postulated that genetic variants may influence an individual's metabolism of arsenic. These may explain for the patients' normal hair arsenic levels.[15]

Since the use of laboratory measures is not uniformly available worldwide and various studies have used different laboratory measure, the WHO advocated a guide for detection of Arsenicosis, which is defined as the use of two major diagnostic criteria: (1) the presence of pigmentary and keratotic skin lesions, and (2) evidence of exposure to elevated levels of arsenic established by history of intake of arsenic contaminated water, or by arsenic concentration in hair or nails.[7] WHO and the Environmental Protection Agency have recommended a threshold of 10µg/L for arsenic in drinking water.[13]

As there is no known specific treatment for Arsenicosis, the emphasis of treatment is placed on the elimination of further consumption of arsenic-contaminated water, cancer investigation and secondary prevention of latent effects through medical surveillance. Surgical excision is used to successfully manage cutaneous malignancy in the setting of arsenicosis.[9] Studies showed that retinoids have been helpful in treating arsenic-induced cutaneous lesions and in reducing the risk of further cutaneous and internal malignant transformation.[9]

A well-balanced diet with folic acid and selenium supplementation has been suggested to lessen the effects of arsenic toxicity.[9] Moreover, antioxidants such as vitamins C and E may be given to decrease oxidative stress.[17] Studies have shown that these antioxidants aid in arresting progression of arsenicosis.[15] It has also been recommended that patients have a thorough skin and physical examination every six months as well as annual chest radiograph to monitor progression of disease.[11] These treatment modalities were used in the cases presented.

CONCLUSION

Chronic arsenic exposure of these reported cases is the first two documented and confirmed cases of arsenicosis in the area.[7,9] The elevated arsenic levels in their drinking water source imply that a considerable portion of the community they live in may have also been exposed, which warrants immediate investigation. The government and the health care system may play a role in assisting to provide safe water supply and to promote awareness of arsenic toxicity by educational programs, which may deliver rehabilitation and environmental consciousness to the community.[7]

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