Arsenic-Related Bowen’s Disease, Palmar Keratosis, and Skin Cancer

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Chronic arsenical intoxication can still be found in environmental and industrial settings. Symptoms of chronic arsenic intoxication include general pigmentation or focal “raindrop” pigmentation of the skin and the appearance of hyperkeratosis of the palms and soles of the feet. In addition to arsenic-related skin diseases including keratosis, Bowen’s disease, basal-cell carcinoma, and squamous-cell carcinoma, there is also an increased risk of some internal malignancies. Arsenic-related diseases are common in areas of the world where the drinking water has a high arsenic content. In this paper, we describe a 35-year-old male patient who had arsenic-related keratosis, squamous-cell carcinoma in the palmar area of his left hand, and Bowen’s disease on his left thigh. The patient worked in a borax mine for 15 years, so he was exposed to arsenic in drinking water, airborne arsenic in his workplace, and had direct contact. The patient was treated for 11 months for arsenic-related keratosis until an axillary lymph node metastasis occurred; the lesion was excised and diagnosed to be malignant. Bowen’s disease was detected when the patient was being treated for cancer. No other malignancy was found. The patient is still receiving regular follow-up care. Key words: arsenic, Bowen’s disease, keratosis, skin cancer. Environ Health Perspect 107:687-689 (1999). [Online 6 July 1999] http://ehpnet1.niehs.nih.gov/docs/1999/107p687-689col/abstract.html

Case Presentation

A 35-year-old male patient with a hyperkeratotic lesion on the palm of his left hand was admitted to the SSK Kütahya Hospital 5 years ago. The patient had a history of fatigue, weakness, and weight loss, but no complaints related to the gastrointestinal tract or other systems.

The lesion, located in the palmar area of his left hand, was diagnosed to be arsenic-related keratosis (Figure 1), and treatment with topical medications was initiated.

The patient had been working as a colmanit and arsenic mine cleaner and separator in the Emre-Hisarck borax mine for 15 years, where he received intense borax and arsenic exposure. This borax mine is located in the western part of Turkey and is owned by the government. There is a high arsenic content in the product of the mine—colmanit. Workers are required to wear gloves, but this patient did not wear gloves and did not use a mask to prevent arsenic exposure because of his inadequate knowledge.

The patient was shifted to another position at work to prevent further direct exposure to arsenic. However, because he lived in the same region, his exposure to arsenic continued. There was still a high level of arsenic both in the workplace and in home tap water.

One year after the initial diagnosis, left axillary lymphadenopathy was found, and a biopsy of the left axillary lymph node was performed in The Ankara University Ibon-i Sina Hospital. Histopathologic examination revealed metastasis of a squamous-cell carcinoma (SCC) to the lymph node. The palmar lesion was biopsied again, with the primary focus on axillary malignant disease, but no malignancy was found. A left axillary lymphadenectomy was performed afterward, and all lymph nodes were free of malignancy. A combination of chemotherapy with cyclophosphamide and 5-fluorouracil (5-FU) and radiotherapy (total dose of 6,000 cGy) was then administered to the patient. At the 6-month follow-up, the patient was diagnosed with a new hyperkeratotic lesion on his left thigh, which had been present for 5 months (Figure 2). The patient was then seen by the Epidemiology Study Group of Ankara University, School of Medicine, who were in the area to perform epidemiologic screening. The patient was evaluated regarding acute and chronic arsenic intoxication.

The patient had weakness and fatigue, and had lost 5 kg of body weight over the previous 2 years, but he had no gastrointestinal complaints (nausea, vomiting, or diarrhea). Computed tomography and ultrasonography of the abdomen were normal. No pathological findings were revealed by neurologic examination or electromyography of the patient. Additionally, no abnormalities were found in urinary examination or cystoscopy. The results of the laboratory tests are presented in Table 1.

Multiple biopsies were made from the lesions on the palm and the thigh. The palmar lesion was determined to be arsenic-related keratosis, whereas the lesion on the thigh was found to be pagetoid Bowen’s disease. We performed a systemic search for internal malignancy using physical, hematological, biochemical, and radiological tests. We excised all lesions, including a margin of 2 cm of normal skin. The wounds were closed with full-thickness skin grafts. Findings of the histopathologic examination of the palmar lesion included large and hyperchromatic nucleated epithelial cells with atypical mitosis and evident nucleoli, tumor cells with globes, and spindle nucleoli. The basal membrane was intact, in general, but a focal invasion was noted. The palmar lesion was determined to be a well-differentiated (spindle-cell) SCC, whereas the lesions on the thigh were accepted to be Bowen’s disease with high grade dysplasia. There were no complications in the postoperative period, and the patient was discharged. He was monitored in the first month after the surgery and no abnormality was found.

Discussion

Arsenic is a metal used extensively in the making of glass, alloys, coloring agents, insecticides, and fungicides. Currently, arsenic is employed in metallurgy, agriculture, animal husbandry, and forestry; it is widely distributed in nature, being mainly transported by water in the environment. The industrial

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applications of arsenic account for the majority of use of inorganic and organic arsenic compounds. In an occupational setting, the respiratory tract provides the most common portal of entry for arsenic. Skin and gastrointestinal pathways are also possible (1).

Our patient was exposed to arsenic exposure by ingestion (drinking water, and foods) and by direct contact with colemantine. The drinking water in the area where the patient lived and worked contained 405 μg/L arsenic, with a range of 45–1,210 μg/L. Colemanite (2CaO • 3B₂O₃ • 5H₂O), the mineral that the patient continuously handled for 15 years, contained 50.9% B₂O₃, 21.9% H₂O, 27.2% CaO, and 1,000 ppm (1 g/kg) arsenic. Fifteen years of high arsenic exposure at work may have caused arsenic-related skin cancer. The current standard of the U.S. Environmental Protection Agency (U.S. EPA) for inorganic arsenic in drinking water is 50 ppb (micrograms per liter); the Occupational Safety and Health Administration (OSHA) established a maximum permissible exposure limit (PEL) for workplace airborne arsenic 10 μg/m³ (2). Current U.S. EPA risk analyses predict that beyond the concentration of 50 ppb arsenic in drinking water, lifetime skin cancer risk would increase by 3 or 4 per 1,000 (2).

Arsenic poisoning is usually the result of accidental or homicidal ingestion of insecticides or rodenticides containing copper acetarsenate, calcium arsenate, or lead arsenate. Arsenic trioxide, the most dangerous form of arsenic, is still used in chemistry laboratories and a few industries. This is a soluble powder with an acute lethal dose in humans of 60–120 mg (3). Arsenic reacts with the sulfhydryl groups in certain tissue proteins and thus interferes with a number of enzyme systems essential to cellular metabolism.

Pathologic changes in fatal inorganic arsenical poisoning are fatty degeneration of the liver, hyperemia and intestinal hemorrhages, and renal tubular necrosis. The peripheral nerves often show fragmentation and resorption of myelin, with disintegration of axis cylinders. Gastrointestinal symptoms develop after acute ingestion, followed by a mixed motor and sensory neuropathy after 2–3 weeks. Tendon reflexes are absent or diminished, and atrophy of affected muscles develops rapidly. The patients who present with arsenic poisoning do not have neurological complaints or findings. The symptoms of acute poisoning by oral exposure are vomiting, diarrhea, weakness, prostration, and weight loss (4). Patients who recover from acute poisoning and those with chronic intoxication usually develop skin and mucosal changes, peripheral neurological symptoms, and typical pigmentations in the nails. The cutaneous manifestations appear within 1–4 weeks and consist of a diffuse, dry, scaly desquamation, occasionally with hyperpigmentation, over the trunk and extremities. Hyperkeratoses of the soles of the feet and edema of the face and extremities may also occur. The mucous membranes also show evidence of irritation, for example, conjunctivitis, photophobia, pharyngitis, or irritating cough. About 5 weeks after exposure to arsenic, a transverse white stria, 1–2 mm in width, appears above the lunula of each fingernail (Mees lines). Our patient had a hyperkeratotic lesion in the palmar area of his left hand.

Symptoms of headache, drowsiness, confusion, and convulsions are seen in both acute and chronic intoxication. The extremities show a decrease in sensitivity to touch, pain, and temperature sensation, with a symmetrical "stocking-glove" distribution; distal weakness of grip and wrist drop.

Our patient suffered from weakness, fatigue, and loss of weight, but he had no gastrointestinal complaints. Computed tomography and ultrasonography of the abdomen were normal.

The laboratory findings of acute arsenic poisoning usually consist of moderate anemia and a leukopenia of 2,000–5,000 white blood cells with mild eosinophilia. There is slight proteinuria, and liver function tests show mild abnormalities. Our patient did not have leukopenia, eosinophilia, or proteinuria, and his liver function tests were normal. In urinary examination and cystoscopy, no abnormalities were found. None of the clinical or laboratory manifestations of arsenic poisoning are specific, and the diagnosis depends on analysis of the hair and urine for arsenic. A normal person has an average concentration of 0.05 mg arsenic per 100 mg hair, with a range of 0.025–0.088 mg. Concentrations of arsenic > 0.1 mg/100 mg hair indicate arsenic poisoning.

Because we do not have the facilities to analyze the samples in our laboratories, we...
were unable to determine the arsenic levels in serum, tissue, and urine.

It is difficult to establish the minimal level of arsenic in urine indicating intoxication. Normal persons have been found to excrete between 0.01 and 0.06 mg arsenic/L of urine. Collection of urine for arsenic analysis should be performed after abstaining from eating seafood, which contains arszenobentaine (which is relatively harmless). Although there is considerable overlap, most patients with evidence of arsenic intoxication excrete > 0.1 mg/L; soon after acute exposure, many show concentrations > 1 mg/L (4).

The relationship of arsenic ingestion to palmar and plantar keratoses and to skin cancer has been documented in studies involving wide-scale exposure to known sources of arsenic (5–8). The strongest epidemiologic evidence on the effects of arsenic on the skin was reported in a Taiwanese study performed in an area with high arsenic concentrations in well water (5,6). Jafar et al. (7) reported three cases of skin cancer caused by arsenic poisoning in patients who had lived near tin mines in Malaysia. In Slovakia, skin cancers were reported to be common in areas polluted with arsenic (8). Arsenic-related Bowen’s disease has predominantly been found in agricultural workers who use arsenical powders in crop dusting and wine growing (9). Malignant and premalignant skin lesions have been reported among paraquat manufacturing workers (10,11). Studies have demonstrated a significant dose–response relationship with the duration of exposure (11,12).

Inorganic arsenic is a carcinogenic agent for the respiratory system, skin, liver, and bladder. In epidemiologic studies in different countries, a positive association between arsenic and the prevalence of skin cancer has been reported (7,8,13).

Inorganic arsenic compounds in drinking water, exposure in the workplace, and drug therapy with inorganic arsenicals have been causally related to the development of skin cancer. Smelter employees and other workers exposed to arsenic trioxide have been shown to have a greatly increased risk of lung cancer (3). Increased mortality from bronchial carcinoma has been found in chemical workers in the production of inorganic arsenicals. Exposure in the past has been heavy and has been predominantly to arsenic trioxide; in smelter workers, exposure patterns are mixed, and other suspected carcinogens are frequently present. Data from other than occupational sources support the carcinogenic role of arsenic for lung cancer, bladder cancer, and liver angiosarcoma (14).

The site of lesions was also typical for arsenic-related skin cancer. Arsenic exposure is a well-known cause of skin cancer, but for this case, we believe that chronic and direct contact of arsenic with the skin at the site of lesion should be overlooked.

Malignant transformation of arsenic-related keratoses is quite rare. In this case, either a malignant transformation of arsenic-related keratoses or synchronous initiation of both diseases may be possible. Bowen’s disease is an intraepidermal SCC of the skin or mucous membrane that pursues a slow and relatively benign course (horizontal or intraepidermal growth) over a period of years, but may progress to invasive SCC (vertical growth). Arsenic, ultraviolet light (UV), radiation, psoralen, and psoralen plus UV light of A wavelength (PUVA) may have a role in the etiology of Bowen’s disease (15–17). In Bowen’s disease, lesions may be found in areas of the skin and mucous membranes including the nailsbeds, palms, and soles. Individual lesions of Bowen’s disease tend to persist for many years without progression to invasive carcinoma. If untreated, 5–15% will present invasion and/or metastasis. Statistical studies do not support a relationship between Bowen’s disease and internal cancers (18). The relationships among arsenic exposure, punctuate keratoses, and internal malignancies are less documented, although highly suggestive (19). Subsequent reports did not support that palmar and plantar keratoses could be markers of systemic cancer (20,21). In our patient, no primary focus for internal malignancy was detected.

In conclusion, the presented case is an important example of arsenic-related skin disease. One should always be concerned about malignancy in such cases. Although it is yet unproven, direct contact with arsenic may be hazardous and should be avoided. Presence of arsenic in the environment (water, food, etc.) should be closely monitored. For this purpose, an epidemiologic study to determine the effects of arsenic and borax on public and environmental health has been initiated by the Public Health Department of Ankara University Medical School in Turkey; Turkey is the greatest borax producer in the world after the United States.

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