

Chronic Arsenicism From Chinese Herbal Medicine

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Chronic arsenicism is associated with cutaneous manifestations, including palmoplantar keratoses, pigmentary anomalies, and nonmelanoma skin cancer. It occurs most commonly following exposure to inorganic arsenic in contaminated drinking water or occupational contact, though medicinal exposure also has been reported. We present a case of a Chinese woman living in the United States with cutaneous manifestations of chronic arsenicism due to a 5-year history of Chinese herbal medicine ingestion.

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The use of medicinal arsenic for treatment of a variety of infectious and neoplastic conditions was introduced in 1786 (Fowler solution). With the discovery of arsenic's multisystem toxic effects, including cutaneous and visceral malignancies, therapeutic use has declined over the past half century.¹ In the United States, arsenic trioxide is approved by the US Food and Drug Administration to induce remission and consolidation in patients with acute promyelocytic leukemia who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy. Arsenic, however, remains a common ingredient or contaminant in a number of Chinese and Indian herbal medicines. Although patients may obtain these medicines abroad, arsenic also has been detected in Chinese² and Indian Ayurvedic³ herbal preparations available in the United States. We describe a case of a patient

with chronic arsenicism presenting with cutaneous manifestations due to ingestion of a Chinese herbal medicine.

Case Report

A 42-year-old Chinese woman living in the United States presented with a 1-year history of thick skin on her palms and soles, and dark spots on her body. She denied a family history of similar findings, personal history of well water ingestion, or occupational exposure to arsenic. She was previously diagnosed with hereditary palmoplantar keratoderma based on clinical presentation. The patient's past medical history was significant for subtype M4 (myelomonocytic) acute myelogenous leukemia (AML), which had been diagnosed 5 years prior to presentation. The patient received 2 cycles of induction chemotherapy with idarubicin hydrochloride and cytarabine liposome, followed by 4 cycles of high-dose cytarabine consolidation chemotherapy that resulted in complete remission of her AML 6 months after diagnosis. At the time of presentation, her only medication was a Chinese herbal preparation, which she had been taking since her diagnosis of AML. The medicine was sent to her by a sister living in China and was made by a Chinese herbalist to prolong remission of her AML.

Physical examination revealed numerous punctate atrophic papules within yellow keratotic plaques over the palms and soles that were more prominent on weight-bearing skin (Figures 1 and 2). Her skin had diffuse, ashy gray, hyperpigmented patches with superimposed hypomelanotic macules on the trunk, most notable on the abdomen and chest, including nipple-areolar complexes (Figure 3). Transverse white lines were noted on her fingernails. There were no lesions clinically suggestive of cutaneous malignancy. Her abdomen was soft with no organomegaly or palpable masses. Results of a neurologic examination were nonfocal. Her complete blood count, electrolytes, and liver transaminase levels were within reference range. Results of an electrocardiogram were normal. Laboratory results revealed

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Figure 1. Punctate keratoses on the palm.



Figure 2. Thick yellow plaques with punctate keratoses on the plantar foot.

a blood arsenic level of 56.1 $\mu\text{g/L}$ (reference range, 0.0–62.0 $\mu\text{g/L}$).

Given the clinical examination and elevated urine arsenic level, the diagnosis of chronic arsenicism was made. The patient was asked to obtain the ingredients of her Chinese herbal medication from her herbalist, which revealed arsenic as a primary ingredient. She has since discontinued use of this medicine, and her skin and nail findings have nearly resolved.

Comment

Inorganic arsenic exposure occurs most often through ingestion of arsenic-contaminated drinking water or food. Occupational exposure to arsenic through

nonferrous metal mining and smelting, pesticide application, coal or wood combustion, and waste incineration also is well-recognized.⁴ Chronic arsenicism has been less frequently reported in patients with medicinal exposure to arsenic from Chinese herbal medicines,⁵⁻⁷ Indian Ayurvedic or homeopathic herbal remedies,⁸⁻¹⁰ Korean herbal medicines,¹¹ and Laotian herbal medicines.¹² In most cases of chronic arsenicism from Chinese herbal medicines that have been reported in the English language literature, patients received the medicines as treatment for asthma during the 1950s and 1960s.^{5,13} Some of these cases have been only recently diagnosed.^{6,7}

While there are reports of chronic arsenicism from ingestion of Indian herbal medications,^{8,10} we



Figure 3. Diffuse ashy hyperpigmentation intermixed with raindrop hypopigmentation on the abdomen (A). Hypopigmented macules with background ashy hyperpigmentation also were present on the abdomen (B).

are aware of only one report of chronic arsenicism caused by ingestion of a Chinese herbal medicine within the past 25 years, a Korean woman with long-term ingestion of a traditional Chinese herbal medicine for neurocysticercosis who presented with hemolytic anemia.¹⁴ Our case describes a woman living in the United States with cutaneous manifestations of chronic arsenicism due to Chinese herbal medicine ingestion.

Cutaneous manifestations of chronic arsenicism include patchy hyperpigmentation; raindrop hypopigmentation; arsenical keratoses, especially of the palms and soles; Mees lines; Bowen disease; squamous cell carcinomas; and basal cell carcinomas. Hyperpigmentation was not observed in 14 Chinese

patients with chronic arsenicism who ingested Chinese proprietary medicines known to contain inorganic arsenic for asthma during the 1950s and 1960s in Singapore. It has been hypothesized that hyperpigmentation is more common in patients who are exposed to arsenic through drinking water as opposed to medicines.⁵ Hyperpigmentation was a prominent feature of our patient's examination, and it also has been observed in other patients with chronic arsenicism from traditional Chinese herbal medicines.⁷

Chronic arsenicism often results in multisystem disease, including gastrointestinal distress, peripheral neuropathy, anemia, vascular disease, portal hypertension, and renal insufficiency,^{15,16} and is

associated with increased risk of malignancies, especially of the skin, lungs, and genitourinary system.⁶ In one study, 7 of 17 Chinese patients with long-term arsenic exposure (most from Chinese herbal medicines) developed one or more cutaneous squamous cell carcinomas, 55% of squamous cell carcinomas (6/11) arising from preexisting keratotic lesions (n=4) or Bowen disease (n=2) and 45% of squamous cell carcinomas (5/11) arising de novo.⁵ Chronic arsenic exposure has been shown to cause chromosomal abnormalities and single-stranded DNA breaks, suggesting a possible mechanism for malignant degeneration.¹⁷

Cutaneous manifestations of chronic arsenicism often are observed before visceral malignancies develop. Pigmentary changes, along with development of palmoplantar keratoses, probably precede the appearance of nonmelanoma skin cancer by more than a decade in most patients⁵; recognition of skin changes may allow for early diagnosis and treatment of skin and visceral malignancies. Our case illustrates that 24-hour urine arsenic levels may be more useful than blood arsenic levels to demonstrate chronic exposure.¹⁵ Dermatologists should be aware of the characteristic cutaneous manifestations of chronic arsenicism and thoroughly explore patient histories, including use of herbal medicines, to discover the source of arsenic exposure when chronic arsenicism is suspected.

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