Imiquimod Cream 5% for the Treatment of Arsenic-Induced Cutaneous Neoplasms

Cheryl Lundeberg Lonergan, MD; Elizabeth Kaufman McNamara, MD; Kelly M. Cordoro, MD; Kenneth E. Greer, MD

Long-term exposure to arsenic has been linked to the development of numerous cutaneous neoplasms including arsenical keratoses, basal cell carcinomas (BCCs), and squamous cell carcinomas (SCCs). We report a patient with a remote history of psoriasis treated with arsenic who subsequently developed more than 40 nonmelanoma skin cancers as well as arsenical keratoses. This patient had a remarkable response to imiquimod cream 5% applied once daily to affected areas for 6 weeks with complete resolution of all cutaneous neoplasms and no evidence of recurrence in more than 3 years of clinical surveillance.

Cutis. 2010;85:199-202.

Case Report

An 84-year-old man presented to the dermatology clinic with numerous growths of unclear duration on both sun-exposed and sun-protected areas of the trunk and extremities. The patient reported a history of arsenic use approximately 70 years prior for the treatment of psoriasis. He stated that he was instructed to instill arsenic-laden eye drops into both eyes once daily until swelling of the eyes was produced, which required approximately 10 days of daily use per treatment episode. He recalled that he underwent numerous treatments over 5 years that ultimately cleared his psoriasis. The patient's medical history was remarkable for coronary artery disease, hypertension, and colon cancer. His daily medications included digoxin, simvastatin, enalapril maleate, aspirin, furosemide, metoprolol, and nitroglycerin. Physical examination revealed 41 erythematous, hyperkeratotic, 5- to 25-mm papules and plaques clinically consistent with keratoses and squamous cell carcinomas (SCCs) on the arms, legs, and trunk (Figure 1A), as well as numerous 3- to 6-mm hyperkeratotic papules on the palms (Figure 2) and soles. Histopathologic review of scout biopsies obtained from general sites of involvement revealed both in situ and invasive SCCs. Specifically, one biopsy obtained from the left thumb was reported as SCC in situ with a lichenoid infiltrate consistent with an arsenical etiology. Mohs micrographic surgery was subsequently utilized to treat 2 aggressive SCCs of the left thumb and right superior helix. However, there were too many remaining cutaneous neoplasms to attempt to treat them individually in an expeditious manner. Therefore, topical field treatment with imiquimod cream 5% was instituted once daily for 6 weeks to each involved anatomic location. This treatment resulted in complete clinical resolution of all remaining cutaneous neoplasms, including the arsenical keratoses (Figure 1B). The patient remained free of disease during more than 3 years of clinical monitoring.

Comment

Arsenic has been used as a medicinal agent for hundreds of years and was introduced into the US Pharmacopeia in 1850.[1] Classified as a group 1 carcinogen by the International Agency for Research on Cancer,[2] arsenic exposure can occur through medications; contaminated substances such as well water; or occupational exposures such as mining, carpentry, agriculture, and the manufacture of computer microchips.[1,3,4] Fowler solution, Pearson solution, Donovan solution, and Asiatic pills were all arsenic-containing medications once used for the treatment of asthma,

Drs. Lonergan and Greer are from and Dr. Cordoro was from the Department of Dermatology, University of Virginia Health System, Charlottesville. Dr. Lonergan also is from Anne Arundel Dermatology, PA, Glen Burnie, Maryland. Dr. Cordoro currently is from the Division of Pediatric Dermatology, Department of Dermatology, University of California, San Francisco. Dr. McNamara was from the University of Virginia School of Medicine, Charlottesville, and currently is from the Department of Dermatology, Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina.

The authors report no conflict of interest.

Correspondence: Cheryl Lundeberg Lonergan, MD, 810 Landmark Dr, Ste 217-219, Glen Burnie, MD 21061 (drlonergan@aadermatology.com).

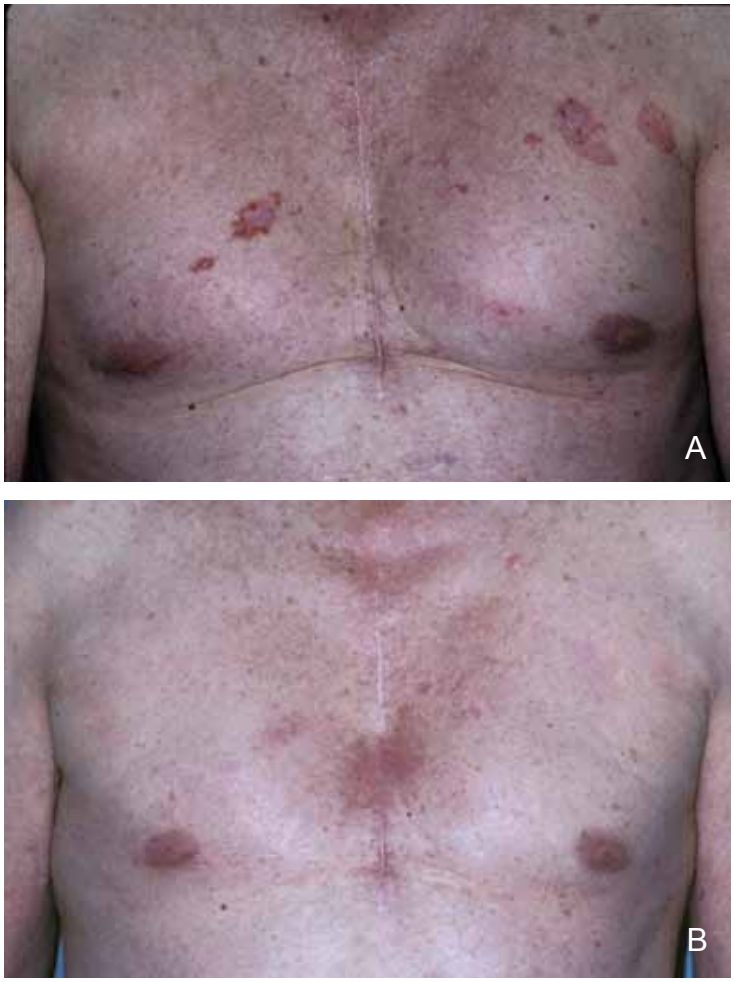

Figure 1. Multiple erythematous hyperkeratotic plaques on the chest clinically consistent with squamous cell carcinoma in situ (A). Clinical clearance of arsenic-induced cutaneous neoplasms following topical treatment with imiquimod cream 5% (B).

psoriasis, syphilis, and other infections. According to the US Environmental Protection Agency, the maximum contaminant level for arsenic in drinking water is 10 ppb,[5] and chronic arsenicalism may be seen following intake of as little as 400 mL of Fowler solution.[1] Once ingested, inorganic arsenic is taken up by red blood cells and distributed to the liver, kidneys, spleen, lungs, intestines, and skin,[1,2] and is detoxified by the liver through a process of reduction and methylation.[4]

Long-term exposure to arsenic is associated with the development of neoplasms of the skin, lungs,

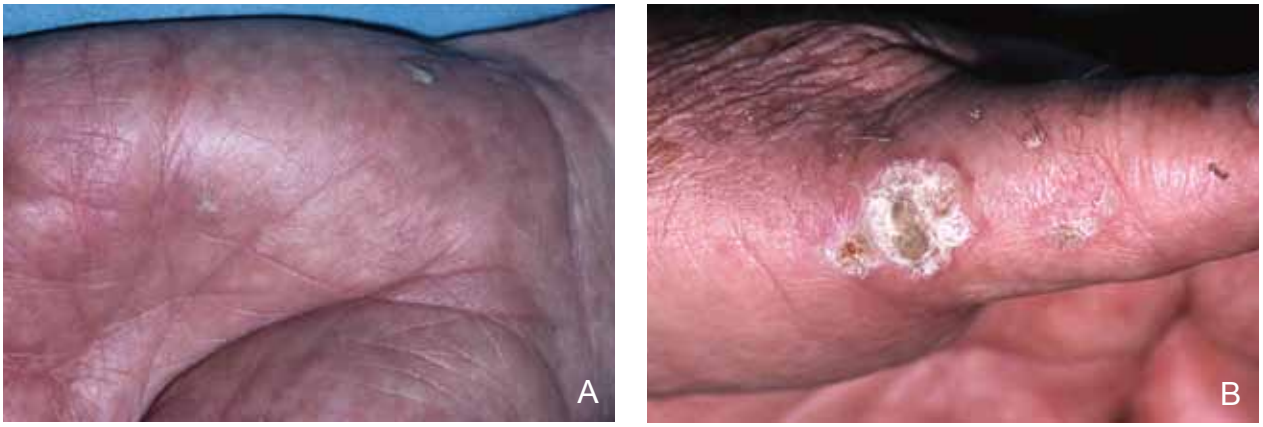

Figure 2. Hyperkeratotic papules on the hand consistent with arsenical keratoses and squamous cell carcinoma (A and B).

liver, urinary tract, and hematopoietic system. Although the exact mechanism of arsenic-induced neoplasms is not known, arsenic has been shown to cause chromosomal abnormalities and single-strand breaks in DNA.[6,7] Additionally, arsenic can induce gene amplification that may upregulate oncogenes.[8] On the skin, arsenic exposure is associated with the formation of arsenical keratoses, basal cell carcinoma (BCC), SCC, and rarely Merkel cell carcinoma.[1,4,9-13] Arsenic-induced cutaneous neoplasms often are widespread, and a distinguishing feature of these lesions is the presentation on sun-protected areas.[7,14] It is believed that the widespread distribution of these neoplasms reflects the diffuse uptake of arsenic in tissue following exposure. They generally are found on the palms, soles, extremities, and trunk.[14,15] Arsenical keratoses typically are hyperkeratotic, punctate, firm papules measuring 2 to 10 mm in diameter that are preferentially located in a palmoplantar distribution as well as other sites of friction.[1] A distinguishing feature of arsenical keratoses is the lack of pits in the skin upon removal.[8] However, they also may present as scaly, erythematous, or hyperpigmented plaques that can be located on the trunk, extremities, genitalia, and eyelids.[1] Bowen disease can occur in the setting of chronic arsenic exposure, particularly in sun-protected areas, and there is a risk for development of invasive SCC in these lesions. Invasive SCC that develops within Bowen disease in patients with a history of arsenic exposure can be aggressive with an increased risk for metastasis.[1] Bowen disease is characterized by full-thickness epidermal atypia with overlying parakeratosis, and arsenic-induced Bowen disease presents in a similar manner. Basal cell carcinomas that arise in the setting of arsenic use tend to be multiple and can clinically resemble Bowen disease.[1] Histologically, BCC patterns associated with arsenic can include all variations such as superficial, nodular, adenoid, reticulated, and pigmented.[1] Arsenic-induced BCCs, however, may have vacuolated cells, dyskeratosis, multinucleate giant cells, nuclear atypia, and increased atypical mitoses.[1,15] Arsenical keratoses are characterized by compact parakeratosis overlying acanthosis with mild epidermal dysplasia, and histopathology may include vacuolated keratinocytes as well as a chronic inflammatory infiltrate in the upper dermis.[1,16] The absence of dermal solar elastosis may be an important histologic characteristic. In general, however, there are few histologic findings distinguishing arsenic-induced Bowen disease, SCC, and arsenical keratoses from UV radiation–induced equivalents.[1]

Treatment of arsenic-induced cutaneous neoplasms is similar to standard cutaneous neoplasms, including surgical excision, cryosurgery, electrodesiccation and curettage, oral retinoid therapy, and topical chemotherapy. Arsenical keratoses and SCC in situ may respond well to acitretin[9]; however, mucocutaneous adverse effects and laboratory abnormalities can limit the use of this treatment.[12] Surgery is highly effective, but it is costly and time consuming when targeting large numbers of neoplasms. Imiquimod cream 5% has been successfully used for the treatment of superficial BCCs, actinic keratoses, and Bowen disease (cutaneous SCC in situ), though the use of imiquimod cream 5% in the treatment of Bowen disease is not currently approved by the US Food and Drug Administration.[17-20] Imiquimod activates macrophages by binding to cell surface receptors, including toll-like receptor 7.[21] This binding increases the release of proinflammatory cytokines, including interferon-α; tumor necrosis factor α; and IL-1, IL-6, IL-8, and IL-12, which leads to an increase in a type 1 helper T cell (T_H1) cell-mediated immune response.[21-23] This T_H1 cell-mediated immune response can effectively target nonmelanoma skin cancer as well as viral infections.[21,23] In addition, imiquimod cream 5% induces epidermal Langerhans cells to mature into fully functioning antigen-presenting cells.[21] Imiquimod cream 5% also has been reported in the literature to be an effective treatment of arsenic-induced cutaneous neoplasms.[11] In that reported case, the patient underwent treatment once daily with imiquimod cream 5% as tolerated for 8 weeks. The patient experienced clearance of the lesions and had no recurrence or progression of the imiquimod-treated lesions over a 2-year surveillance period.[11]

Conclusion

We report a patient with a remote history of arsenic exposure who subsequently developed numerous cutaneous neoplasms, primarily arsenical keratoses and in situ and invasive SCCs. Topical treatment with imiquimod cream 5% was instituted once daily for 6 weeks leading to complete clinical resolution of the neoplasms without recurrence in more than 3 years of clinical surveillance. The use of imiquimod cream 5% is a novel, convenient, noninvasive approach to the treatment of arsenic-induced cutaneous neoplasms.

REFERENCES

1. Schwartz RA. Arsenic and the skin. *Int J Dermatol.* 1997;36:241-250.
2. Chen YC, Guo YL, Su HJ, et al. Arsenic methylation and skin cancer risk in southwestern Taiwan. *J Occup Environ Med.* 2003;45:241-248.
3. Wagner SL, Maliner JS, Morton WE, et al. Skin cancer and arsenical intoxication from well water. *Arch Dermatol.* 1979;115:1205-1207.

4. Kurokawa M, Ogata K, Idemori M, et al. Investigation of skin manifestations of arsenicism due to intake of arsenic-contaminated groundwater in residents of Samta, Jessore, Bangladesh. *Arch Dermatol.* 2001;137:102-103.
5. Fact sheet: drinking water standard for arsenic. US Environmental Protection Agency Web site. http://www.epa.gov/safewater/arsenic/regulations_factsheet.html. Updated January 2001. Accessed March 12, 2010.
6. Wong SS, Tan KC, Goh CL. Cutaneous manifestations of chronic arsenicism: review of seventeen cases. *J Am Acad Dermatol.* 1998;38(2, pt 1):179-185.
7. Boonchai W, Green A, Ng J, et al. Basal cell carcinoma in chronic arsenicism occurring in Queensland, Australia, after ingestion of an asthma medication. *J Am Acad Dermatol.* 2000;43:664-669.
8. Schwartz RA. Premalignant keratinocyte neoplasms. *J Am Acad Dermatol.* 1996;35(2, pt 1):223-242.
9. Watson K, Creamer D. Arsenic-induced keratoses and Bowen's disease. *Clin Exp Dermatol.* 2003;29:46-48.
10. Lien HC, Tsai TF, Lee YY, et al. Merkel cell carcinoma and chronic arsenicism. *J Am Acad Dermatol.* 1999;41:641-643.
11. Boonchai W. Treatment of precancerous and cancerous lesions of chronic arsenicism with 5% imiquimod cream. *Arch Dermatol.* 2006;142:531-532.
12. Yerebakan O, Ermis O, Yilmaz E, et al. Treatment of arsenical keratosis and Bowen's disease with acitretin. *Int J Dermatol.* 2002;41:84-87.
13. Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol.* 2004;50:714-721.
14. Hsueh YM, Cheng GS, Wu MM, et al. Multiple risk factors associated with arsenic-induced skin cancer: effects of chronic liver disease and malnutritional status. *Br J Cancer.* 1995;71:109-114.
15. Yeh S, How SW, Lin CS. Arsenical cancer of the skin. histologic study with special reference to Bowen's disease. *Cancer.* 1968;21:312-339.
16. Yeh S. Skin cancer in chronic arsenicism. *Hum Pathol.* 1973;4:469-485.
17. Mackenzie-Wood A, Kossard S, de Launey J, et al. Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol.* 2001;44:462-470.
18. Geisse J, Caro I, Lindholm J, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. *J Am Acad Dermatol.* 2004;50:722-733.
19. Szeimies RM, Gerritsen MJ, Gupta G, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from a phase III, randomized, double-blind, vehicle-controlled, clinical trial with histology. *J Am Acad Dermatol.* 2004;51:547-555.
20. Patel GK, Goodwin R, Chawla M, et al. Imiquimod 5% cream monotherapy for cutaneous squamous cell carcinoma in situ (Bowen's disease): a randomized, double-blind, placebo-controlled trial. *J Am Acad Dermatol.* 2006;54:1025-1032.
21. Stanley MA. Imiquimod and the imidazoquinolones: mechanism of action and therapeutic potential. *Clin Exp Dermatol.* 2002;27:571-577.
22. Dahl MV. Imiquimod: a cytokine inducer. *J Am Acad Dermatol.* 2002;47(suppl 4):S205-S208.
23. Persaud AN, Shamuelova E, Sherer D, et al. Clinical effect of imiquimod 5% cream in the treatment of actinic keratosis. *J Am Acad Dermatol.* 2002;47:553-556.