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Chromated copper arsenate–treated wood: a potential source of arsenic exposure and toxicity in dermatology

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ABSTRACT

Arsenic-contaminated drinking water presents a serious health hazard in certain geographic locations around the world. Chromated copper arsenate, a pesticide and preservative that was used to pressure treat residential lumber in the United States beginning in the 1940s and was banned by the Environmental Protection Agency in 2003, poses a potential source of arsenic exposure and toxicity. In this study, we review the clinical manifestations of arsenic intoxication with the focus on dermatologic manifestations. Dermatologists should be aware that although chromated copper arsenate-treated wood for residential use was banned in 2003, the exposure risk remains. Long-term follow up is necessary to detect arsenic induced cutaneous and visceral malignancy in patients with history of arsenic exposure.

Arsenic is a naturally occurring heavy metal substance. It is rarely found in its pure elemental state; rather combining with various elements to form inorganic and organic arsenic. Inorganic arsenic compounds are more toxic than organic arsenic compounds (Jomova et al., 2011; Schuhmacher-Wolz et al., 2009). Inorganic arsenic was designated a human carcinogen by the U.S. Environmental Protection Agency (EPA) in 1986 (Levine et al., 1988).

Arsenic has been used both as a therapeutic agent in medicine and as a poison for more than 2,000 years. Arsenic preparations were used in the 18th and 19th centuries as antipyretics, antiseptics, caustics, antispasmodics, depilatories, sedatives, tonics, and as an agent to combat trypanosomiasis (Haller, 1975; Waxman and Anderson, 2001). In the 1700s, Thomas Fowler developed a 1% solution of arsenic trioxide in potassium bicarbonate that was used empirically for the treatment of dermatologic diseases such as dermatitis, pemphigus, and psoriasis. Fowler's solution also was used to treat asthma and chorea (Aronson, 1994; Kwong and Todd, 1997).

The effect of Fowler's solution on leukocytes was noted after a patient with chronic myelogeneous leukemia was found to have a dramatic decline of white blood cells when treated with Fowler's solution (Cutler and Bradford, 1878). In 2000, the Food and Drug Administration approved arsenic trioxide infusion for induction of remission and consolidation in patients with acute promyelocytic leukemia who were refractory to, or had relapsed from, retinoid and anthracycline chemotherapy, and whose leukemia had yielded the presence of the t(15;17) translocation or *PML/RAR-α* gene expression (Trisenox, 2000).

Environmental exposure to arsenic can either be due to natural occurrence (air, soil, water) or as a result of anthropogenic activities. The largest source of environmental exposure to arsenic is dietary, such as seafood and poultry. Fortunately, arsenic compounds found in these sources are essentially harmless in the form of organic arsenic (Jomova et al., 2011). In contrast, millions of people in Bangladesh, India, Taiwan, China, southeast Asia, and North and South America are exposed to inorganic arsenic via drinking water due to high concentrations from geogenic sources (Berg et al., 2001; Tapio and Grosche, 2006). Recently, traditional Chinese and Tibetan herbal products, fortified with arsenic for its therapeutic purposes, have been found to present a serious health hazard (Martena et al., 2010; Wong et al., 1998).

Exposure to arsenic and its various compounds has well-documented detrimental effects on human health. Inorganic arsenic is far more toxic than organic arsenic due to generation of free radicals and oxidative stress resulting in cellular damage and cell death (De Vizcaya-Ruiz et al., 2009; Shi et al., 2004). Furthermore, it alters DNA repair and methylation patterns, resulting in enhanced cell

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proliferation, gene amplification, and suppression of *p53* (Jomova et al., 2011; Kitchin, 2001; Schuhmacher-Wolz et al., 2009).

Manifestations of arsenic toxicity depend on the dose, route, age at exposure, and duration of exposure. Measurements of arsenic level in blood, urine, hair, and nails have been used as indicators for exposure (Jomova et al., 2011). Testing for and interpreting results of arsenic levels can be complicated. Therefore, direct communication with the testing laboratory and consultation with a toxicologist is recommended. Blood levels are usually not a reliable marker because arsenic is metabolized rapidly (Tam et al., 1979). Both organic and inorganic arsenic are excreted by the kidney and quantification as well as speciation of the urinary arsenic is reliable for the diagnosis of acute and chronic arsenicism (Goldman, 2016; Jomova et al., 2011). Total urine arsenic level is generally less than 10 μg/g creatinine in individuals without occupational arsenic exposure and who have not consumed fish, as a single meal of fish can increase total urine arsenic to more than 1,000 μg/L.

In an emergent situation suspicious for acute arsenic intoxication, a spot urine arsenic can be obtained. However, urine creatinine in the spot sample must also be obtained to correct for the urine concentration. A diagnosis of acute arsenic exposure is supported when urine arsenic concentration is greater than or equal to 50 μg/L, or 100 μg/g creatinine in the absence of recent fish intake. A 24-hour urine arsenic is a more accurate measurement than a spot urine arsenic to assess for chronic arsenic exposure. It is important to remind patients to avoid fish for 48 to 72 hours before sample collection. As discussed previously, urine arsenic typically is less than 10 μg/g creatinine in individuals without occupational or dietary arsenic exposure (Goldman, 2016). Hair and nail arsenic levels are used to document chronic exposure (Chen et al., 2005a). However, variable results often are reported due to lack of standardized testing (Goldman, 2016).

Although rarely mentioned, dermatologic manifestations can be present in acute arsenic toxicity. In one study, it was noted that 56% of acute arsenic poisoning victims exhibited dermatologic findings such as, in decreasing order of frequency, conjunctival hemorrhage, facial edema, acral desquamation, maculopapular eruptions in intertriginous areas, and transient flushing (Uede and Furukawa, 2003). Dermatologic findings of chronic arsenic exposure such as Mee's line of the nail, palmar-plantar hyperkeratosis, and focal or generalized raindrop hyperpigmentation in sun-protected areas have been well documented (Wong et al., 1998). Interestingly, macular hypopigmentation was noted in studies from Asia (Miki et al., 1982; Wong et al., 1998).

The most common arsenic-induced skin cancers include Bowen's disease (BD), basal cell carcinoma (BCC), and squamous cell carcinoma (SCC). Results from a case–control study found that in individuals with toenail arsenic concentrations above the 97th percentile, the adjusted ratios for SCC and BCC were 2.07 (95% confidence interval [CI] [0.92, 4.66]) and 1.44 (95% CI [0.74, 2.81]) respectively, when compared with those at or below the median concentration (Karagas et al., 2001). Clinical characteristics suggestive of arsenic-induced skin cancer include occurrence on sun-protected areas as well as multiple and recrudescent lesions (Yu et al., 2001). Identification of palmar-plantar keratosis and BD should raise the suspicion of chronic arsenicism (Allen et al., 1979). The latency period for the development of arsenical keratosis, BD, BCC, and SCC ranges from 15 to 40 years, which underscores the importance of long-term follow up (Wong et al., 1998).

The occurrence of arsenic-induced skin cancer in sun-protected areas is of particular interest. One study found decreased number of Ki 67-positive cells in arsenic-induced BD 2 weeks after ultraviolet B (UVB) irradiation when compared with nonirradiated skin of the same individual. The authors postulate a UVB inhibitory effect on arsenic-induced cell proliferation as a potential explanation for finding skin cancer in sun-protected areas in arsenic exposed individuals (Chai et al., 1997). However, arsenic and UV radiation are known co-carcinogens in animal models (Burns et al., 2004). More recently, it was found that pretreatment of normal human cultured keratinocytes in vitro with arsenic prevents these keratinocytes from undergoing UVA- and UVB-induced apoptosis (Chen et al., 2005b; Sun et al., 2011). It is likely that different molecular signals are activated by arsenic, UVA, and UVB resulting in a complex interplay between them in vivo. For example, a study of *p53* mutations in arsenic-related skin cancers found a higher rate and different types of *p53* mutations when compared with those in UV-induced skin cancer (Hsu et al., 1999). Langerhans cell dysfunction and changes in the cytokine milieu further complicate this already complex relationship (Wang et al., 1991; Yu et al., 1992a; Yu et al., 1992b).

Although melanoma has not been historically associated with arsenic exposure, a case–control study showed an increased risk for melanoma in individuals with elevated toenail arsenic (odds ratio = 2.1, 95% CI [1.4, 3.3]) (Beane Freeman et al., 2004). However, inorganic arsenic compounds inhibit cell proliferation and prevent invasion of human and murine melanoma cell lines in vitro (Hiwatashi et al., 2011). Furthermore, arsenic trioxide has been demonstrated to induce a mitochondrial dependent apoptosis in human uveal melanoma cells (Chen et al., 2010). The relationship between arsenic and melanoma remains to be delineated.

In addition to the skin, virtually all organs can be affected by arsenic due to its effect on the vascular endothelium. Acute arsenic toxicity may cause cardiomyopathy and hypotension, whereas chronic arsenic toxicity may manifest as hypertension and ischemic heart disease (Mumford et al., 2007; Wang et al., 2003). Peripheral vascular disease as well as cerebral infarct also are noted. Gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, and hematemesis are observed in short-term high-dose and long-term low-dose exposure (Jomova et al., 2011). Elevated liver enzymes with portal fibrosis, cirrhosis, and bronchiectasis can be observed (Liu et al., 2002; Mazumder et al., 2005; Rahman et al., 2009). The most typical neurologic manifestation is symmetrical peripheral sensory and motor neuropathy, which may last for years and is only partially reversible (Fincher and Koerker, 1987; Mathew et al., 2010). Based on epidemiologic studies, visceral malignancies involving the lung, bladder, kidney, liver, colon, and bone have been associated with arsenic exposure in a dose–response relationship after a long latency period (Enterline et al., 1995; Gibb et al., 2011).

Management of both acute and chronic arsenic exposure remains supportive and symptom directed. There is no antidote for arsenic intoxication. Two chelation therapies are available in the United States. Dimercaprol, also known as British Anti-Lewisite, is the chelating drug of choice for acute severe arsenic toxicity. Although few data supports the use of chelation therapy in subacute or chronic arsenic poisoning, meso-2, 3-dimercaptosuccinic acid is the preferred agent in the setting of ongoing arsenic exposure. In both acute and chronic arsenic exposure, it is paramount to eliminate further exposure and contamination (Goldman, 2016).

Chromated copper arsenate (CCA), which contains 47.5% hexavalent chromium, 18.5% copper, and 34% inorganic arsenic, is a pesticide and preservative that was used to pressure treat lumber beginning in the 1940s. In the 1970s, CCA was widely used in the United States for outdoor residential wood such as decks, picnic tables, landscaping timbers, fencing, patios, walkways, boardwalks, and playground structures until it was phased out by the EPA in 2003. The history and regulatory events leading to the phasing out of the CCA-treated residential wood product is complicated and beyond the scope of the current discussion. In brief, similar to all other pesticides, CCA is registered under the Federal Insecticide, Fungicide and Rodenticide Act by the EPA. In 2001, the EPA and U.S. Consumer Product Safety Commission received public petitions to ban CCA use in

playground equipment due to potential human health concerns from contacting this chemical residue from the treated wood and surrounding soil (U.S. Consumer Product Safety Commission, 2011). As a result, in February 2002, the manufacturers of CCA voluntarily amended their registrations, requesting the EPA to terminate residential uses of CCA products and canceling their registrations (U.S. Environmental Protection Agency, 2003).

Cancellation of these registrations went into effect in March 2003 (U.S. Environmental Protection Agency, 2003). Although no manufacturer has been able to treat wood with CCA for residential uses since December 2003, the EPA does not prohibit the sale of CCA-treated wood produced before 2003. However, retailers must display a warning label when CCA-treated wood is sold. The Consumer Awareness Program also recommends wearing gloves when handling wood, wearing goggles and masks when sawing and sanding, and never burning CCA-treated wood. Acute and chronic arsenicism have been reported with burning CCA-treated wood (Peters et al., 1983, 1984, 1986).

It is important to remember that along with contaminated ground water and Fowler's solution, CCA-treated wood is a source of significant arsenic exposure. Dermatologists should be aware that although CCA-treated wood for residential use was banned in 2003, exposure risk remains, especially as airborne particulates have been found at incendiary or construction sites. Long-term follow up is necessary to detect arsenic-induced cutaneous and visceral malignancy in patients with history of arsenic exposure.

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