Arsenic Toxicity in Hawaii: A Case Report and Review

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The presence of seemingly unexplained peripheral neuropathy in a sick patient warrants persistent delving into the medical, social and especially occupational history. Bearing this in mind, we have an interesting case to present.

Case Presentation

The patient was a 36-year-old man who had been diagnosed as having peptic ulcer disease and the presence of *helicobactor pylori* in an EGD biopsy specimen 3 months earlier. He was admitted to the hospital because of an acute onset of epigastric pain that began that morning. The patient was admitted to the regular medical ward and the gastroenterologist who had been following the patient for his PUD was consulted. The gastroenterologist recommended medical therapy empirically for the ulcers. He believed the patient required a stat EGD since a follow-up EGD done 2 weeks earlier had been negative for ulcers. An H2 blocker medication for *helicobactor pylori* was started. He required 75 mgs of meperidine i.m. for his severe abdominal pain.

The abdominal pain persisted; further work-up included an upper GI series, which showed no ulcers but did show some evidence of duodenitis, and a CT scan of the abdomen that was negative. Laboratory work-up included stool cultures, pancreatic enzymes, sickle cell screen, hepatitis screen, porphyria screen, liver function tests, and ESR, all of which were negative.

The patient described his abdominal pain as being intermittent, excruciating, either localized in the epigastric region, the left lower quadrant, or sometimes everywhere; it was associated with nausea but no vomiting. On physical examination, there was no rebound or guarding but mild to moderate tenderness to palpation could be demonstrated. He continued to complain of abdominal pain throughout his hospital course, and he required a constant regimen of pain control including Demerol, Dilaudid, Darvocet, Percocet, and even a PCA pump with low-dose morphine.

The patient's abdominal pain work-up was completed without any significant findings. He was discharged to outpatient care with pain medication, an H2 blocker, and medication for *helicobactor* prophylaxis. He was instructed to return for follow-up in a clinic in a couple of days.

When he reported to the clinic, he still complained of severe abdominal pain and had taken all of the pain medicine given at discharge. During this visit, a 24-hour urine heavy-metal screen was obtained. The report came back negative for lead and mercury but was positive for arsenic at 865 mcg/liter (normal < 100). To confirm this urine arsenic finding, pubic hair analysis for arsenic was done and it also returned positive at 5.6 microgram/gram of hair (* 75% have less than 0.03 to 0.3 mcg/gm hair, 20% are between 0.3 to 3mcg/gm hair, 5 % are up to 4 mcg/gm hair.) A more detailed diet and work history was obtained. He was treated as an outpatient for arsenic toxicity with penicillamine. However, he presented himself again to the clinic with the same, severe abdominal pain before penicillamine therapy. He was again admitted to the hospital for treatment with dimercaprol or BAL (British Anti-Lewisite), which entails intramuscular injections every 4 hours. The patient improved clinically, the repeat 24-hour urine-arsenic level was < 35 mcg/liter, and the arsenic content in the hair was down to 1.3 mcg/gram of hair.

The patient continued to be followed closely as an outpatient. His abdominal pain reoccurred with a fluctuating course. Additional work-up revealed a negative colonoscopy, a negative nerve conduction test and electromyelogram and negative lab tests, including urine and hair arsenic levels. Many questions were raised: Was this definitely arsenic toxicity? If so, what was the source of the arsenic? Were the GI symptoms related to the arsenic toxicity?

The Sources of Arsenic

Arsenic is ubiquitous in nature and the 20th most common element in the earth's crust[1]. Arsenic is present in saltwater and seafood. Fish and shellfish contain a relatively high concentration of arsenic; this is relatively nontoxic and is readily excreted through urine[2]. Urinary arsenic levels may be increased as much as tenfold after eating a large seafood meal[1]. Notably, arsenic also is found in well water[3].

Historically arsenic has been used in medicines[4] and currently organic arsenicals are still being used in the treatment of certain protozoan diseases. It is also an ingredient in veterinary medicine[5]. Arsenic has been used in feed for poultry, cattle and swine to improve the nutritional status of animals[6]. Furthermore, arsenic has been a constituent of drugs such as opium[5]. Industrial use of arsenic has been a major source of worker exposure. In 1973, the National Institute for Occupational Safety and Health estimated that 1.5 million

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people were potentially exposed to arsenic during the course of their work[7]. Smelter workers were at increased risk for potential arsenic exposure. A study of smelter workers indicated increased mortality—mostly secondary to lung cancer—proportional to their exposure to arsenic[8].

Arsenic is used in many commercial products; it is used as an additive in metal alloys to increase hardening and heat resistance, in the manufacture of glass, in wood preservatives, in lead-plating, and in various types of paints including fresco, tempera, watercolor, and oil paints[5].

Arsenic also is used in making silicon microfilm[4], light-emitting diodes in watches[9], and in salt-impregnated materials for fires to produce multicolored flames[10]. Arsenic also plays a major role in agriculture: Pesticides, herbicides, fungicides, weed/tree killers, fly killers, rodenticides all contain arsenic because of its effectiveness and low cost[11]. The use of arsenic as a desiccant of cotton comprises 15% of the U.S. market for arsenic trioxidel. Significantly in our case, arsenic trioxide is a commonly used agent in the treatment of wood against termites. The wood used in the construction industry in Hawaii often is pressure-treated with this compound.

Clinical Manifestations of Toxicity

The clinical manifestations of arsenic toxicity vary widely and are dependent on the duration of exposure, level of the dose (if ingested), whether intake is acute or chronic, and on the chemical compound of the arsenic. The 3 forms of toxic arsenic are the trivalent salt, pentavalent salts, and arsine gas[12]. Elemental arsenic is not toxic[12]. Pentavalent salts are found in the earth's crust and are prevalent in foods; they are less toxic than the trivalent salts which tend to accumulate in the body more readily. Arsine gas is the most toxic and is frequently fatal.

Acute toxicity can occur with arsine gas poisoning or with massive doses of ingested arsenic. The symptoms of acute arsenic intoxication are apparent within 30 to 60 minutes, but death usually does not occur until approximately 24 hours later[13]. A garlicky odor in the breath and stool may be apparent. The patient might complain of a metallic taste in the mouth[14].

Arsine gas poisoning is usually overwhelming and usually leads to death. Initial symptoms include: Fever, headache, nausea, vomiting, epigastric pain, dysuria, and explosive diarrhea. Hemolytic anemia also occurs as the arsenic binds to red blood cells; cyanosis and hypoxia could ensue. Shock with intractable vascular collapse and encephalopathy can occur, and myocardial damage and bone marrow suppression.

Acute ingestion of arsenic is usually more insidious in it's manifestations. Severe gastrointestinal involvement is the hallmark of acute ingestion. Symptoms can include nausea, vomiting, profuse watery diarrhea and colicky abdominal pain[14]. Dysphagia secondary to the toxic damage to the esophageal lining can occur, as well as dehydration and electrolyte abnormalities. Other gastrointestinal manifestations include jaundice, hepatomegaly, hepatic enzyme abnormalities and even pancreatitis.

Almost every organ system can be involved. Cardiorespiratory findings include EKG abnormalities such as QT prolongation, nonspecific ventricular arrythmias and sagging of the ST segment[15,16,17]. Pulmonary edema, bronchial pneumonia and pericarditis can occur. Neurological manifestations include seizures, encephalopathy, headache, vertigo, and a sensorimotor neuropathy which occurs 10 days to 3 weeks after the exposure[13]. Hematologically, anemia is the most common (normochromic-normocytic, hemolytic). Other findings include leukopenia, aplastic anemia, leukemia, and thrombocytopenia[14]. Renal failure and proteinuria secondary to cortical necrosis can occur and a case of severe rhabdomyolysis with the CPK elevated to 31,350 U/L in a fatal arsenic trioxide poisoning has been reported[13].

Chronic arsenic exposure is associated with several other abnormalities in addition to some of the features of acute arsenic poisoning. One of the most characteristic abnormalities of chronic toxicity involves the skin. Dermatologic manifestations include: Hyperpigmentation (arsenic melanosis), brawny desquamation, hyperkeratosis (especially of the palms and soles), alopecia, dermatitis, folliculitis and "rain drop" depigmentation[12,14]. Skin cancers have been known to appear in 5% to 10% of people with chronic exposure to arsenic. The cancers can appear 5 to 25 years later and appear mostly on the trunk and upper extremities. Histologically, the lesion can be either squamous cell or basal cell[12].

The content of arsenic in nails and hair has been used for diagnosis of chronic exposure. Aldrich-Mees lines (white transverse bands across fingernails and toenails) can be seen 4 to 6 weeks after exposure[14,19]. An elevated concentration of arsenic in the hair is a sign of chronic toxicity. The upper limit of normal content in individuals not exposed to arsenic is said to be approximately 5mg/kg but the arsenic content in hair can vary depending on environmental and nutritional factors[20].

Other manifestations of chronic toxicity include squamous cell carcinoma of the lung and liver abnormalities such as hepatocellular carcinoma, post necrotic cirrhosis and hemangioendothelioma. In Taiwan, peripheral vascular (Blackfoot) disease has been associated with high exposure to arsenic in well water[12].

Other Reported Cases in Hawaii

In the search for other cases of arsenic toxicity in Hawaii, we contacted the pathology departments of most of the major hospitals in Oahu, as well as Smith Kline Laboratory, Diagnostic Laboratory Services of Hawaii and the Hawaii Department of Health. There were several cases reported to the Department of Health, but all of the reports were dismissed as high urinary arsenic levels secondary to seafood ingestion rather than to arsenic toxicity. One patient at Kaiser Permanente Medical Center presented with peripheral neuropathy. Work-up revealed elevated urinary arsenic levels 1300 mcg/l and 372 mcg/l (normal < 100 mcgA) and an elevated hair arsenic level of 151 mcg/100 gram of hair (normal 0-65 mcg/100gram). The source of his arsenic exposure was unknown.

As a result of our investigation, there were no other reports of arsenic toxicity in Hawaii that were documented by positive urine and hair analysis.

Diagnosis and Treatment

A carefully detailed history regarding the possible source of the exposure is extremely important when considering arsenic toxicity as a diagnosis. In addition to the history and physical, laboratory tests are useful—some more than others. Serum arsenic level is often not helpful because of rapid clearance. A 24-hour urine collection is useful, especially for documenting acute arsenic intoxication. Arsenic is excreted through the kidney at a rate of 30% to 70% in a 24-hour period[21]. Toxic levels might be missed if there is a delay between

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the time of exposure and the time of evaluation. In acute ingestion, abdominal radiographs might be useful because arsenic, a heavy metal, will show up radiographically[22].

In chronic exposure, analysis of nails and/or hair is helpful though the arsenic content of hair is affected by nutritional and environmental factors. Arsenic is present in hair and nails 2 to 4 weeks after ingestion[5]. One paper reported analysis of arsenic in other biological fluids, such as gastric and vesicular fluids that accumulate higher levels as compared to pleural and pericardial fluids[23]. There is no standardized value or a definitive test that diagnoses the arsenic toxicity absolutely, although urine arsenic levels greater than 200 mcg/l and hair arsenic levels greater than 65mcg/100 grams of hair can be used as a presumptive evidence of an increased arsenic load[21].

Treatment should be directed in 2 ways: Chelation therapy to increase excretion of arsenic and supportive and symptomatic therapy for the organ systems involved in the toxicity. The Poisindex[24] at the Hawaii Poison Center recommends the following treatment: "For acute massive arsenic ingestion, cardiac and respiratory support using compressors and ventilators, as in any other critical patient is recommended. This should be followed by gastric decontamination with gastric lavage and an absorbent such as activated charcoal, or a cathartic magnesium citrate or a sorbitol solution. Alkalinization of the urine might be helpful in preventing deposition of red blood cell breakdown products in renal tubular cells when hemolysis is occurring."

Chelation therapy is recommended in symptomatic patients known to have ingested arsenic and in asymptomatic patients who have a documented urinary arsenic level greater than 200 mcg/l. Dimercaprol is the first line of treatment. The dose ranges from 3 to 5 mgAkg i.m. every 4 to 12 hours until the symptoms abate or another chelator is substituted. One author recommends tapering the dose but continuing administration of dimercaprol until the urinary excretion is less than 50mcg/24 hours[1]. Dimercaprol is an effective chelator but has some disadvantages. The intramuscular injections can be painful, and there are many adverse effects such as mild systemic shock, tachycardia, hypertension, vomiting, convulsions, headache, nausea, vomiting and anorexia. A prior injection with epinephrine might alleviate some of systemic effects[25]. D-Penicillamine is an oral chelator found to be effective. The usual dose is 25 mg/kg given 4 times a day up to one gram/day. The 3 short-term adverse effects have not been reported, but long-term effects of penicillamine have included fever, leukopenia, thrombocytopenia, eosinophilia and renal toxicity. Another agent, 2,3-dimercaptosuccinic acid (DMSA), appears to be a promising method of treatment, although currently it is approved only for use in lead-poisoning in children. DMSA for adult arsenic treatment is still under investigation and, therefore, must be obtained from the Regional Poisons Unit[27].

Summary

As mentioned at the beginning of this article, many questions were raised in our one particular case including the problem of verifying true arsenic toxicity and in determining the source of the exposure. In our case, there was a markedly elevated concentration of arsenic in samples of pubic hair and in the sample of urine.

While arsenic toxicity can present with GI symptoms, we felt that in this particular case the association of the abdominal pain with arsenic toxicity was unlikely. For one, the patient's symptoms persisted despite apparent adequate treatment for arsenic toxicity. Also, the usual symptom of chronic arsenic toxicity is peripheral neuropathy (which was not documented in our case) and not abdominal pain. After the exhaustive diagnostic workup, we felt that this patient had irritable bowel syndrome and that the discovery of arsenic toxicity was serendipitous.

In regards to the etiology of the toxicity, the patient's occupation involved working in the construction industry for a number of years. He indicated a definite exposure to termite-treated wood throughout that period. Wood for building houses, etc. is commonly pressure-treated with an arsenic-based compound; therefore, this source of occupational exposure appears to be a likely one.

Another remotely possible source was the ingestion of contaminated illicit drugs. Cases of the use of illicit drugs laced with various toxic agents such as cyanide and strychnine have been reported. Although our patient required analgesics not commensurate with his symptoms, he categorically denied any use of "street" drugs. The random urine drug screen for such was negative. The patient also claimed he was subjected to a series of random urine drug screens at the job and all had been negative.

In conclusion, our patient represented what appeared to be a well-documented case of arsenic toxicity. However, further investigation was needed as to whether the source might have been prolonged exposure to chemically treated wood. In that eventuality, medical practitioners need to consider arsenic toxicity in their differential diagnosis of patients presenting, in particular, with peripheral neuropathy of unknown etiology, and should obtain an appropriate occupational history.

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REFERENCES

1. Gorby Michael S. Arsenic poisoning. *West J Med.* 1988;149:308-305.
2. Malachowski Marie E. An update on arsenic. *Clin in Lab Med.* 1990;10:3:459-472.
3. Franzblau Alfred, Lilis Ruth. Acute arsenic intoxication from environmental arsenic exposure. *Arch Environ Health.* 1989; 44:6:385-390.
4. Graef John W, Lovejoy Jr. Frederick H. Heavy metal poisoning, arsenic. *Harrison's Principle Int Med.* 12th ed. New York, Mc Graw-Hill Inc. 1991;2182- 2183.
5. Schoolmeester W. Lawrence, White Douglas R. Arsenic poisoning. *South Med J.* 1980;73:2:198-208.
6. Fishbein L. Natural non-nutrient substances in the food chain. *Sci Total Environ.* 1972;1:211-244.
7. Occupational Exposure to Inorganic Arsenic. U.S. Dept of Health, Education, and Welfare, National Institute for Occupational Safety and Health, Washington. U.S. Government Printing Office. 1973;l6.
8. Pinto SS, Enterline PE, Henderson V, et al. Mortality experience in relation to a measured arsenic trioxide exposure. *Environ Health Perspect.* 1977; 19:127-136.
9. Arena, JH. Inorganic chemical-type insecticides. *Poisoning: Toxicology, Symptoms, Treatment.* Springfield, Ill. Charles C. Thomas Publisher, 3rd ed. 1974;l20-138.
10. Nelson KW. Industrial contributions of arsenic to the environment. *Environ Health Perspect.* 1977;19:31-34.

11. Kaye Sidney. Arsenic. *Handbook of Emergency Toxicology.* 5th ed Illinois. Charles C. Thomas Publisher. 1988;199-205.
12. Louria Donald B. Trace Metal Poisoning, Arsenic, Cecil Textbook of Medicine. 19th ed. Philadelphia. W.B. Saunders Company. 1992;2364-2365.
13. Tallis G A. Acute lead arsenate poisoning. *Aust NJ J Med.* 1987;19:730-732.
14. Campbell Jack P, Alvarez Joseph A. Acute arsenic intoxication. 1989; 40:6:93-9715.
15. Fennell JS, Stacy WK. Electrocardiographic changes in acute arsenic poisoning. *Ir J Med Sci.* 1981;150:338-9.
16. Glazener FS, Ellis JG, Johnson PK. Electrocardiographic findings with arsenic poisoning. *Calif Med.* 1966;109:158-62.
17. Barry KG, Herndon EG. Electrocardiographic changes associated with acute arsenic poisoning. *Med Ann DC.* 1968;109:158-62.
18. Sanz Pere et al. Rhabdomyolysis in fatal arsenic trioxide poisoning. *JAMA.* Dec 1989; 262:23:3271.
19. Hutton JT Christians BL. Sources, symptoms, and signs of arsenic poisoning. *J Fam Pract.* 983;17:423-6.
20. Poklis Alphonse, Saady Joseph: Arsenic poisoning: acute or chronic? suicide or murder? *Am J of Forensic Med Pathol.* 1990;11:3:226-232.
21. Fuortes Laurence. Arsenic poisoning ongoing diagnostic and social problem. *Postgrad Med.* Jan 1988;83:1:233-244.
22. Gray JR, Khalil A, Prior JC. Acute arsenic toxicity—an opaque poison. *Journal of the Can Assoc Rad.* Aug 1989; 40:226-227.
23. Quatrehomme Gerald et al. Acute arsenic intoxication: forensic and toxicologic aspects. *J Forensic Sci.* 1992; 37:4:1163-1171.
24. Poisindex (R) Toxicologic management. Hawaii Poison Center.
25. Goldfrank Lewis, Howland Mary Ann, Kirsten Robert H: Heavy Metals, Arsenic, in Toxicologic Emergencies. 4th ed. California. Appleton and Lange. 1990;617-624.
26. Stokinger Herbert E. Arsenic. *Patty's Industrial Hygiene and Toxicology.* 3rd ed. New York, Wiley. 1978-79;1517-1531.
27. Jollife DM, Budd AJ, Gwilt DJ. Massive acute arsenic poisoning. *Anaesthesia.* 1991; 46:288-290.

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