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Cod intake masquerading as arsenic toxicity

In diagnosing arsenic poisoning, occupational or environmental exposure to arsenic must be considered, and urine arsenic levels must be interpreted with caution to ensure that chelation treatment is not given without cause.

ABSTRACT: Arsenic toxicity is a rare but well-documented cause of a common presenting complaint: peripheral neuropathy. The definitive diagnosis relies on urine arsenic levels, which must be fractionated into inorganic and organic species, the latter of which is not harmful but can be elevated transiently following the consumption of seafood. We present a case in which a patient presented with progressive sensorimotor neuropathy with diagnostic uncertainty. Spot urine arsenic testing revealed an elevated total, but not inorganic, arsenic level after the patient had consumed seafood the night before. Chelation therapy was initiated out of caution but was likely not warranted. This case highlights the importance of thoughtful clinical interpretation in conjunction with support from poison control to aid in the diagnosis and management of heavy metal toxicity.

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This article has been peer reviewed.

Arsenic is a naturally occurring element in the Earth's crust and is typically combined with oxygen, chlorine, sulfur (inorganic arsenic), or carbon (organic arsenic).[1,2] Inorganic arsenic has been recognized as toxic since ancient times and is classified as hazardous under the Canadian Environmental Protection Act.[3-5] While organic arsenic is generally less toxic, its effects on humans remain under-researched.

The most common source of human-ingested arsenic is drinking water.[6] Because arsenic dissolves readily, water that has come into contact with contaminated rocks and soil may be a source of toxicity. The ambient concentration of arsenic in surface water and groundwater in Canada is very low, usually 1 to 2 μg/L.[7-9] However, localized high concentrations of arsenic have been found in well water from several regions of British Columbia, almost always associated with arsenic-containing bedrock formations or contamination from mining or fracking.[8] Seafood may also contain arsenic, but it is predominantly the less harmful organic form.[10]

Exposure to high levels of inorganic arsenic can lead to acute or chronic health effects, including gastrointestinal distress, hepatotoxicity, neuropathy, and skin changes.[2,3,11,12] A symmetric, sensorimotor polyneuropathy that can sometimes mimic Guillain-Barré syndrome is one of the most prominent symptoms of arsenic poisoning; it can develop 1 to 3 weeks after acute high-dose poisoning or insidiously from chronic low-level exposures.[1,11,13] Biological samples for measuring arsenic include urine (most common), blood, hair, and nails. BC labs report the speciation of arsenic as both total and inorganic rather than speciating the organic subtype. An elevated urinary total arsenic level with a low inorganic arsenic level typically indicates nontoxic organic arsenic. This most commonly results from seafood consumption; even a single meal of fish, shellfish, or seaweed can significantly increase urine arsenic levels.[14-16] Based on the results of the longitudinal Canadian Health Measures Survey, the upper threshold for total urine arsenic is 27 μg/L—including both organic and inorganic forms.[17] For reference, a single serving of blue mussels or codfish can result in urinary excretion of more than 300 μg of arsenic over the 72 hours following consumption.[18,19]

The primary management of chronic arsenic poisoning involves identifying and eliminating the source. In the setting of acute toxicity in critically ill patients, early parenteral chelation therapy is recommended in addition to supportive care.[20] However, in BC, antidotes can be difficult to access due to challenges maintaining adequate stocks to ensure timely administration over a vast geographical area. In a 2003 study, less than 50% of urban BC hospitals had an adequate stock of the antidote to treat arsenic toxicity.[21] In addition, chelating agents are not without their own

host of adverse effects, including depletion of vital elements such as copper and zinc.

We present a case in which a spot urine arsenic test led to the detection of elevated total, but not inorganic, arsenic levels, which resulted in potentially unnecessary chelation therapy. This article illustrates the importance of clinical expertise in guiding the interpretation of data, particularly as it relates to an uncommon toxidrome.

Case data

A 63-year-old female presented to an emergency department in Vancouver with a 6-month history of progressive weakness and neuropathic pain. She had had more than 20 presentations to hospital over the preceding 6 months, with a multitude of symptoms, including unresolving pain, diarrhea, and depression. Her symptoms had worsened severely in the 2 weeks prior to her presentation at the emergency department, leading to severe neuropathic pain, difficulty ambulating, and an inability to complete her activities of daily living. She also had a history of an unprovoked pulmonary embolism, hypertension, chronic diarrhea, and a bilateral salpingo-oophorectomy. Given her significant functional decline and depressive symptoms, she was admitted as an involuntary patient under psychiatric care.

The patient was seen by the neurology service 2 weeks following her admission. On examination, she was afebrile and vitally stable. Her neurologic examination demonstrated appropriate alertness, attention, and language. Her cranial nerve exam did not show any asymmetry. Examination of her lower extremities showed normal power but reduced proximal muscle bulk and decreased sensation to light touch and pinprick modalities bilaterally in a symmetric, stocking-glove distribution.

The patient underwent electromyography and nerve conduction studies, which demonstrated a length-dependent sensorimotor axonal neuropathy with evidence of active neuropathic denervation. Her lab results demonstrated a normal vitamin B12 level, no monoclonal protein present on serum or urine protein electrophoresis, and a normal ratio of free light chains. Glycated hemoglobin was 5.3%. Serologies for HIV, hepatitis B and C, and syphilis were protective. MRI of the spine did not demonstrate any spinal cord, nerve root, or leptomeningeal process. At the time, a unifying systemic condition (such as a malignant or paraneoplastic syndrome) was favored, given the history of unprovoked pulmonary embolism and significant weight loss, but the differential diagnosis remained broad, including inflammatory, metabolic, and nutritional etiologies. In light of the patient's severe depression and gastrointestinal symptoms, in addition to further workup, a heavy metal screen (including spot urine arsenic levels) was sent from the referring hospital to In-Common Laboratories, an accredited Canadian medical laboratory referral testing service, and was processed at the London Health Sciences Centre. Two weeks later, poison control directly notified the team that the urine total-arsenic-to-creatinine ratio was elevated, at 2133 µmol/mol creatinine (reference range: ≤ 93 µmol/mol creatinine). While speciation of the inorganic arsenic level was underway, the patient was initiated on chelation therapy with 2,3-dimercapto-1-propanesulfonic acid, with support from poison control and toxicology. Notably, only 20 doses were available in the Lower Mainland, and Health Canada Special Access approval was required to mobilize further drug supply from Germany. Special Access application for oral chelating agent 2,3-dimercaptosuccinic acid was approved and made available 4 days after the initiation of chelation therapy, and the patient continued on weight-based dosing at 800 mg by mouth 3 times per day. One week after starting chelation therapy, her inorganic arsenic levels returned to normal, at 18 µmol/mol creatinine (reference range: ≤ 21 µmol/mol creatinine).

An elevated urinary total arsenic level with a low inorganic arsenic level typically indicates nontoxic organic arsenic. This most commonly results from seafood consumption; even a single meal of fish, shellfish, or seaweed can significantly increase urine arsenic levels.

On further history, the patient did not report any history of travel, well-water exposure, use of herbal supplements, exposure to pesticides or herbicides, or changes in where she obtained her poultry, meat, or fish. There were no reports of similar symptoms among her family or neighbors.

Given that organic arsenic levels typically have negligible toxic effects and can be elevated due to the intake of seafood, we elected to send confirmatory tests with 24-hour urine and hair arsenic levels to the Mayo Clinic Laboratories; arsenic was undetectable. With this in mind, we spoke with food services at the admitting hospital and found that the evening before the patient's fractionated urine arsenic levels were sent, she was served cod, which could explain the acute elevation in organic arsenic.

The patient experienced only minimal improvements in her symptoms following initiation of chelation therapy in addition to supportive therapies. She was ultimately transferred to an inpatient neuromusculoskeletal rehabilitation centre for ongoing care. Given the degree of diagnostic uncertainty, she received a sural nerve biopsy, which demonstrated an active inflammatory neuropathy with areas of focal microvasculitis. She was later treated empirically with 5 days of IV methylprednisolone and IV immunoglobulin with a subsequent extended prednisone taper and continued to experience subtle improvements in her strength and sensation.

Discussion

Peripheral neuropathies are among the most common neurological diseases, affecting 77/100 000 individuals per year and up to 30% of older adults.[22] In Western countries, the most common causes of peripheral neuropathy are diabetes, toxic exposure (e.g., alcohol, chemotherapy), and inflammatory or immune-mediated conditions. In the US, between 10% and 20% of cases are classified as idiopathic.[22] Necessary laboratory testing includes complete blood count, erythrocyte sedimentation rate, comprehensive metabolic panel (blood glucose, glycated hemoglobin, renal function, and liver function), thyroid function, vitamin B12 level, and serum protein immunofixation. However, in a subacute or rapidly progressive peripheral neuropathy, a more extensive history and tailored laboratory testing should be considered on a case-by-case basis.

Chronic low-level inorganic arsenic exposure is a known carcinogen and has been associated with an increased risk of bladder, lung, and skin cancer.[23] In the acute period, individuals may experience skin changes, hepatotoxicity, cardiovascular dysrhythmias, and/or sensorimotor neuropathy.[11] However, the symptoms of arsenic toxicity can vary widely depending on the chronicity and dose of exposure. According to the World Health Organization, there is no universal definition of the disease, which challenges our ability to make an efficient and accurate diagnosis.[24] Worldwide, hundreds of millions of people are chronically exposed to clinically meaningful inorganic arsenic concentrations in their environment, which stresses the value of an accurate and thorough history of environmental and occupational exposures.[25,26] Kawasaki and colleagues described the delayed development of predominantly sensory polyneuropathy in patients exposed to environmental arsenic following mining activities in Toroku, Japan.[27]

The diagnosis of arsenic toxicity can be further evaluated by obtaining arsenic concentrations from biological samples, including urine, blood, hair, and fingernails. A 24-hour urine arsenic collection is considered the gold standard but can be cumbersome to obtain. Thus, the most commonly used measure is spot urine arsenic levels, which are typically normalized to the concentration of creatinine. An important consideration in using urine arsenic testing is speciation of organic and inorganic forms to avoid misdiagnosis of arsenic poisoning in a patient exposed to the nontoxic organic form. Most laboratories run the total urine arsenic level and perform reflexive speciation only if the total level is elevated.

There are notable challenges in both access to and interpretation of timely diagnostic test results, as well as the initiation of treatment, which highlights the need for improved education and clinical support for physicians who face this clinical scenario.

In addition, speciation results can be reported in different ways (e.g., total and inorganic, organic and inorganic, methylated and inorganic), which complicates the clinician's ability to interpret the results. Additionally, BC practitioners have to send urine arsenic tests to a central laboratory for processing (London Health Sciences Centre, London, Ontario; In-Common Laboratories, North York, Ontario). In the case we have reported, 15 days had elapsed between collection of samples and receipt of a preliminary deranged result.

If the urine total-arsenic-to-creatinine ratio is elevated, with low or normal levels of inorganic species, the urine arsenic was likely derived from the nontoxic organic metabolites. The most likely sources of organic arsenic include dietary sources such as seafood, shellfish, wild mushrooms, and rice, which can elevate the total, but not inorganic, level of urine arsenic.[10,14,15,28] However, reflexive assays may take time to be reported, which can lead to premature initiation of chelation therapy. The inappropriate use of 2,3-dimercapto-1-propanesulfonic acid can lead to adverse effects, including gastrointestinal problems, skin reactions, cytopenias, and elevated liver enzymes, as well as deficiency of other elements, such as copper and zinc. In addition, provincial availability of the arsenic antidote, dimercaprol, is limited, particularly in rural areas, where antidote supplies are more likely to be insufficiently stocked. This situation may place poisoned patients at risk of avoidable morbidity or mortality.

To mitigate these adverse effects, tests for arsenic levels should be ordered only in conjunction with a thorough history of any exposures to aid in developing a pretest probability for acute or chronic arsenic toxicity. Urine arsenic levels should always be speciated and interpreted with the support of clinical toxicologists or poison control to reduce the risk of acting prematurely on false-positive results.

Summary

Peripheral neuropathy is a common presenting complaint with a host of etiologies. Rarely, this can be caused by heavy metal toxicity. A symmetric, sensorimotor polyneuropathy is one of the most prominent symptoms of arsenic poisoning and can develop from both acute and chronic exposure. To make the diagnosis of arsenic poisoning, clinical suspicion must remain high in patients with occupational or environmental exposures, but urine arsenic levels must be interpreted with caution to ensure that chelation treatment is not given without cause. We have presented a challenging diagnostic case of severe axonal peripheral neuropathy where elevated total organic arsenic levels were detected, likely in the context of seafood intake. Given the debilitating neuropathy that caused paraplegia and dysautonomia with severe orthostasis, which prevented the patient from engaging in any active rehabilitation therapy, chelation therapy was initiated promptly based on the urine total-arsenic-to-creatinine ratio. After inorganic arsenic levels returned

to normal 1 week later, chelation therapy was deemed unnecessary. There are notable challenges in both access to and interpretation of timely diagnostic test results, as well as the initiation of treatment, which highlights the need for improved education and clinical support for physicians who face this clinical scenario. ■

Competing interests

None declared.

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