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VIA MEDICA

Ischemic stroke as a consequence of acute hemolytic anemia following arsenic poisoning

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Case presentation

We present the case of a patient who developed acute hemolytic anemia following arsenic poisoning. This case posed many diagnostic challenges. As a result of the hemolytic anemia, the patient experienced an ischemic stroke of the left hemisphere of the brain during hospitalization.

Initially, a 24-year-old male was admitted to the internal medicine department and then transferred to the hematology department. The patient had developed acute anemia with a high hemolysis index. His medical history included dark red urine (bilirubinuria), yellowing of the skin, and weakness. On the day of admission, the patient had lost consciousness on his way to the bathroom. Upon hospital admission, his condition was described as moderate but stable, cardiopulmonary functional, and normal vesicular sounds. Over the previous week he had noted dark urine, yellowing skin, and progressive weakness. White blood cell count (WBC) was 7.93 G/L, red blood cells (RBC) = 1.52 T/L, indicating acute normocytic anemia — hemoglobin (Hgb) = 53 g/L, hematocrit (Ht) = 14.6%, mean corpuscular volume (MCV) = 96.1 fl, iron (Fe) = 41.9 umol/L, ferritin 0.002 nmol/L, platelets (PLT) = 239 G/L, C-reactive protein (CRP) = 171.33 nmol/L, hyperbilirubinemia — total bilirubin = 261.69 umol/L, Direct Antiglobulin Test (DAT) — IgG 3+. Computed tomography (CT) of the chest revealed no abnormalities in the lungs, lymph nodes, or skeletal system. Abdominal and pelvic CT showed splenomegaly (143 mm in the largest dimension), no focal changes, and no lymph node abnormalities. No destructive changes indicative of hyperplasia were found in the skeletal system. Doppler ultrasound of the veins and arteries of the lower limbs showed no deviations from the norm. Treatment with methylprednisolone (1,000 mg i.v. for 10 days with gradual dose reduction) was initiated with limited clinical effect. Over the following days of hospitalization, hemolysis increased, and hemoglobin levels decreased, despite transfusion of 16 RBC units (RBC = 1.21 T/L, total bilirubin = 150.5 umol/, Hgb = 42 g/L, Ht = 13.4%). Therapeutic plasma exchange (TPE) was used, but unfortunately did not yield results. During further hospitalization, symptoms of ischemic heart disease were noted (D-Dimer = 29.20 mg/L, Troponin I = 1.33 ng/ml. In differential diagnosis, bacterial and viral infections, paroxysmal nocturnal hemoglobinuria (PNH), and thrombotic thrombocytopenic purpura (TTP) were excluded. Heart ultrasound showed thinning of the interatrial (IAS) and interventricular (IVS) septum with possible shunting. Over the following days, the patient reported headaches and blurred vision. Neurological, ophthalmological and otolaryngological consultations revealed no deviations from the norm. Due to partial vision loss in the right eye, CT and magnetic resonance imaging (MRI) of

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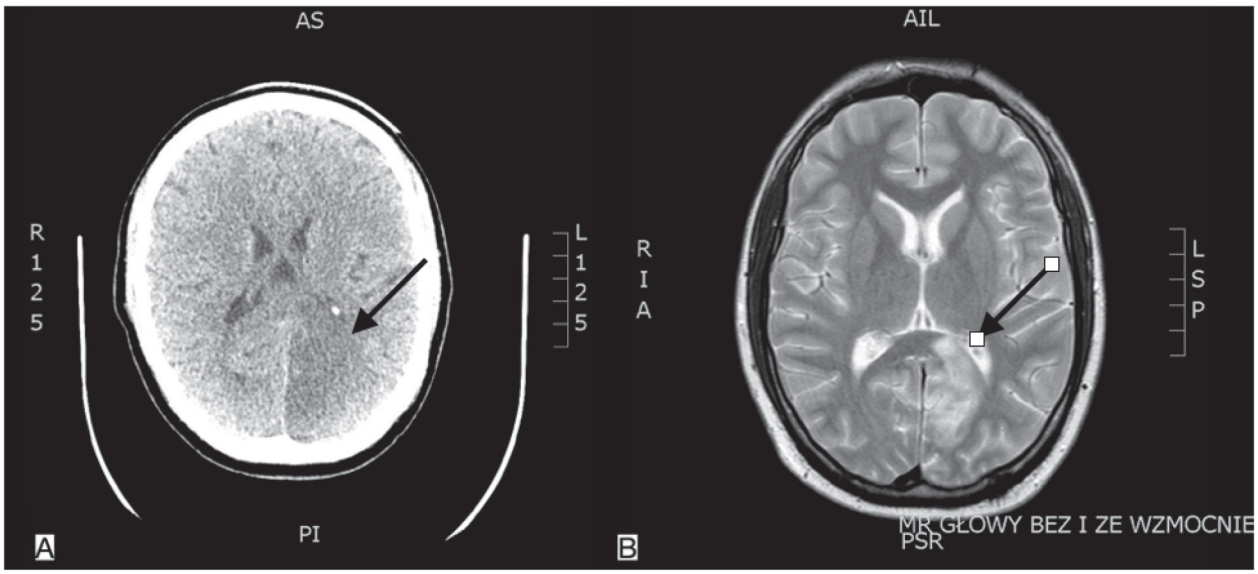

Figure 1A. Non-contrast head MRI: hypodense area with characteristic fresh ischemic change — stroke focus visible in brain's left hemisphere (in parietal and occipital lobes); **B.** Head MRI with contrast

the head were performed. Head MRI revealed an ischemic focus in the left parietal-occipital lobe (Figure 1). A neurological consultation confirmed an ischemic stroke of the brain.

Due to the lack of treatment effects, a decrease in morphological parameters, and a deteriorating clinical condition, the patient was qualified for emergency treatment with rituximab 375 mg/m^2 — 4 doses. This treatment improved the patient's clinical condition, morphology, and hemoglobin levels (WBC = 8.52 G/L, RBC = 2.98 T/L, Hgb = 10.8 g/L, mean corpuscular volume (MCV) = 105.4 fl, PLT = 271 G/L, total bilirubin = 18.8 umol/L. Bone marrow biopsy after rituximab treatment showed no abnormalities.

On the 12th day of hospitalization, a urine toxicology test for metals was performed. The tested material showed the presence of mercury (Hg) at a concentration of 1.12 ug/L, lead (Pb) at a concentration of 2.25 ug/L, and cadmium (Cd) at a concentration of 1.57 ug/L, all within physiological values, plus arsenic (As) at a concentration of 70.88 ug/L (normal is less than 50 ug/L), which was above the reference range. In follow-up toxicology tests on the 22nd and 23rd days of hospitalization, a decrease in urine arsenic levels to 9 ug/L and 3 ug/L, respectively, was observed. Due to the late identification of the cause of hemolytic anemia, the observed decrease in arsenic concentration in the urine, and an improvement in blood morphology parameters (reduction of hemolysis), chelation therapy was not implemented.

After 39 days, the patient was discharged home in good condition (headaches and blurred vision had subsided), not knowing the circumstances as to where he might have been exposed to arsenic. Due to the suspicion of intentional poisoning, the matter was reported to the police in agreement with the patient.

Discussion

Arsenic (As) belongs to metalloids and is highly toxic in large doses. It is found in groundwater, polluted environments, and food [1]. Arsenic poisoning usually occurs through the consumption of contaminated drinking water, contaminated food and tobacco smoke, and industrial and agricultural processes. Foods such as seafood, fish, poultry, and grains can be sources of arsenic, but its form is less toxic than that found in groundwater. When seeking a potential source of infection in a patient, it is worth taking into account his or her profession i.e. workers in the glass, dyeing, textiles, paper, metal, pharmaceutical and pesticide industries have increased exposure to arsenic compounds.

The disease mainly affects people in South Asia. It is estimated that over 140 million people worldwide are exposed to arsenic poisoning through contaminated drinking water [2]. The author of an article published in 2004 describes the occurrence of cerebellar and brainstem symptoms in Japanese people drinking large amounts of arsenic-contaminated water [3]. Another source of As is plants grown with contaminated groundwater e.g. rice [4]. Significant amounts of arsenic are also found in seafood [5]. In Asian countries, arsenic is often an additive in herbal medicines, which may also contribute to the frequent poisoning in this part of the world [6].

Symptoms of arsenic poisoning are varied and depend on, among other things, the route of administration, the dose, and the duration of arsenic exposure. The higher the dose and the longer the exposure time to arsenic, the greater the risk of developing cardiovascular diseases (e.g. hypertension), internal organ damage (leading to the development of diabetes and liver failure), cancers (mainly lung, kidney, liver, and bladder), irreversible changes in the central nervous system, and skin changes [7, 8].

Arsenic poisoning is also the cause of neurological disorders. Damage to the nervous system by As can manifest in many ways, such as headaches, seizures, and even encephalopathy.

In the case presented here, the patient complained of headaches and visual disturbances. So far, no specific neurotoxic mechanism of arsenic action has been discovered. It is believed that arsenic enhances oxidative stress and mitochondrial dysfunction, decreases acetylcholinesterase activity, and leads to thiamine deficiency [2]. It has been found that arsenic can cross the blood-brain barrier, causing neurotoxic effects [1]. An article in 2016 described the case of a 40-year-old man from India who experienced painful paresthesia of the limbs, weakness, balance and sensory disorders [6].

The presented case of a 24-year-old man who developed hemolytic anemia confirmed to be due to arsenic poisoning through extended toxicological diagnostics, highlights the importance of toxicological tests during the diagnosis of patients in non-toxicological departments. In the presented case, the medical history did not reveal information that could indicate that the patient's condition was caused by arsenic poisoning, and the patient himself, after obtaining toxicological results, could not identify the source of the poisoning. In 2009, a case was described of a 56-year-old man who presented to hospital because of dark red-colored urine [9], as in our case. After several hours, the patient developed fever, jaundice, diarrhea and impaired consciousness. The patient was diagnosed with acute renal failure and hemolytic anemia. The cause of these symptoms was five minutes of inhalation contact with a gas mixture containing arsenic.

In addition, arsenic trioxide is used medically as an anticancer drug in adult patients to induce remission and consolidate acute promyelotic leukemia (APL). The total clearance of As III after a single dose in the range of 7–32 mg (0.15 mg/kg, i.p.) is 49 L/hr, and the renal clearance is 9 L/hr.

Rapid identification of the cause of poisoning, in this case arsenic, would have allowed for targeted treatment and likely prevented the effects of arsenic itself i.e. hemolytic anemia leading to ischemic stroke of the brain.

Article information and declarations

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Authors' contributions
MP — manuscript preparation. IM, TJ, BPB, MN, JJO, KK — data collection. KBJ — supervision, final approval.

Conflicts of interest
The authors declare no conflict of interest.

Ethics statement
Authors obtained patient informed consent for publication.

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Supplementary material
None.

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