CHEST

A 44-Year-Old Woman With Metabolic Acidosis, High Anion Gap, and Delayed Neurologic Deterioration

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A 44-year-old woman was brought to the ED from John F. Kennedy International Airport. The patient was returning with her son from a 3-month visit to Bangladesh. Her journey started with a 4-h flight from Dhaka, Bangladesh to Dubai, United Arab Emirates. She consumed 240 mL of whiskey during the flight. This was followed by a 14-h flight from Dubai to New York. According to the patient's son, she did not consume any alcohol during the second flight. The patient was in her usual state of health with normal mentation throughout her journey. Upon landing, she started complaining of shortness of breath. After disembarking, she was witnessed to have seizure-like activity with involuntary passage of urine, following which she collapsed. The patient was intubated by emergency medical services in the field.

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The patient's medical history was significant for hypertension and depression. She was taking amlodipine and citalopram prior to presentation. She drank 1 pint of whiskey every day and was an active smoker with a 10-pack-year history. She did not have any previous history of seizures or head trauma. She had no family history of seizure disorder. As per her son, she was emotionally disturbed and stressed due to her financial conditions in Dhaka.

Physical Examination Findings

On arrival, the patient was afebrile with a heart rate of 114 beats/min, BP of 141/86 mmHg, respiratory rate of 36 breaths/min, and oxygen saturation of 100% on Fio 100%. She was orally intubated with minimal response to deep painful stimuli. Physical examination, including fundoscopic examination, chest, heart, and extremities, was normal.

Diagnostic Studies

Initial laboratory results included a normal CBC count and the following values: sodium, 147 mEq/L; potassium, 5.3 mEq/L; bicarbonate, 5 mEq/L; chloride, 102 mEq/L; BUN, 7 mg/dL; and creatinine, 1.7 mg/dL. Markers of liver function and D-dimer were normal. Her serum ethanol level was undetectable with negative urine toxicology for cocaine, opiates, phencyclidine, and cannabinoids. Lactic acid was 1.30 mM, and osmolar gap was 10. Arterial blood gas was 6.80/20/573 on FIO_2 100%. Urine analysis for crystals was negative. Her ECG showed sinus tachycardia at 112 beats/min with a normal axis and no ST-T changes. Her chest radiograph

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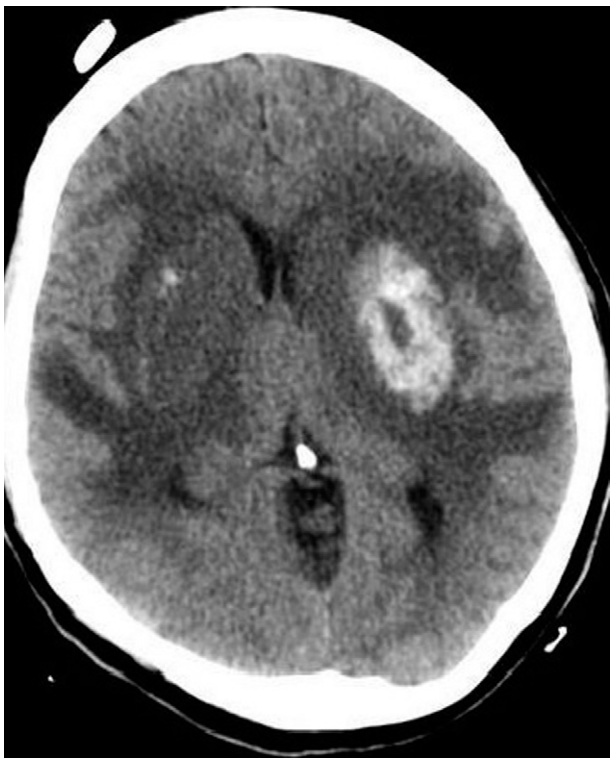

Figure 1 – *CT scan showing bilateral basal ganglia hemorrhage, more prominent on the left.*

showed a normal cardiac and mediastinal silhouette with clear lung fields. A head CT scan failed to show any acute intracranial pathology.

Despite the absence of an osmolar gap, methanol intoxication was suspected. Serum methanol level was tested, and the patient was treated with fomepizole and hemodialysis on admission. The patient required hemodialysis for the next 2 days. Her metabolic acidosis resolved with improvement in her mental status. She was extubated on the seventh day of admission. Methanol level on admission was reported to be 45 mg/dL. The patient admitted consuming illicit alcohol in Bangladesh before boarding the flight. During her second week of hospital stay, while undergoing rehabilitation, she became drowsy and lethargic with deteriorating mental status. Repeat head CT scan showed acute bilateral basal ganglia hemorrhage (more prominent on the left) with surrounding vasogenic edema (Fig 1). Subsequent MRI showed bilateral putaminal hemorrhagic necrosis with surrounding edema (Fig 2).

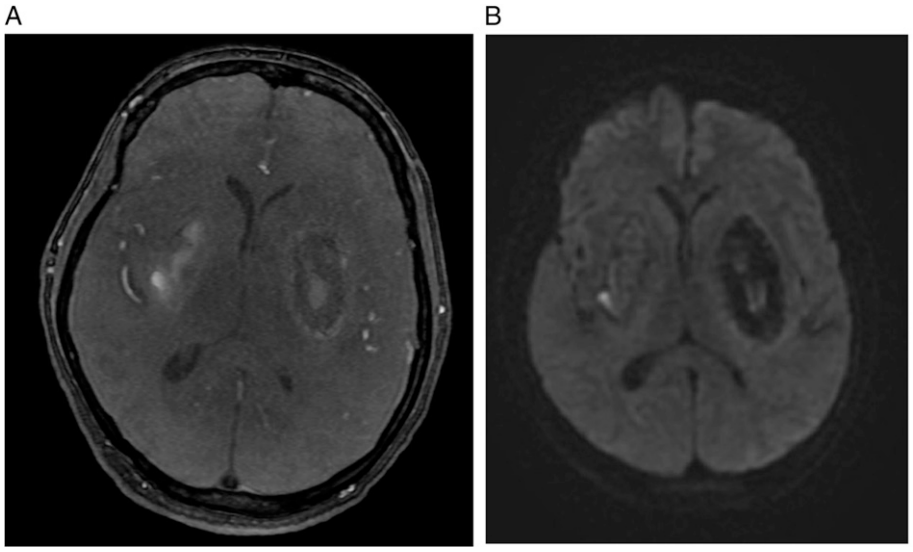

Figure 2 – *A, B, MRI showing bilateral hemorrhagic putaminal necrosis with extensive edema.*

What is the diagnosis?

Diagnosis: Bilateral putaminal necrosis secondary to methanol intoxication

Discussion

High-anion-gap metabolic acidosis is a commonly encountered metabolic abnormality in clinical practice, especially in the ICU setting. The common causes that lead to high-anion-gap metabolic acidosis include lactic acidosis, uremia, diabetic ketoacidosis, salicylate intoxication, and alcohol intoxication (methanol, ethanol, and ethylene glycol). Some of the rarer causes include paraldehyde and isoniazid intoxication.

As opposed to the other causes of high-anion-gap metabolic acidosis, intoxication by any of the three commonly abused alcohols is usually accompanied by a high osmolar gap. It is important to remember that patients who present within 12 to 24 h after intoxication have a high osmolar gap but a relatively low anion gap, whereas patients who present after 24 h have a lower or no osmolar gap but a very high anion gap. These time-related differences are due to the metabolism of the alcohol by the enzyme alcohol dehydrogenase, which metabolizes the alcohol into an aldehyde and finally to an acid. As alcohol starts getting converted to an acid, the osmolarity decreases and the anion gap increases. The only alcohol that gets converted to a ketone and not to an acid is isopropyl alcohol. Thereby, isopropyl intoxication is characterized by high osmolar gap initially, followed by the presence of fruity odor and ketones in the later phase. Isopropyl alcohol intoxication never presents with high-anion-gap metabolic acidosis.

The toxic effects of alcohol intoxication are also mostly mediated by the final acid product resulting from the metabolism of alcohol. Thereby, the treatment of alcohol intoxication focuses on inhibiting the metabolism of alcohol by the enzyme alcohol dehydrogenase and by removal of final acid product by hemodialysis. Fomepizole is commonly used to inhibit the metabolism of alcohol. In several countries where fomepizole is not readily available, IV ethanol is used to inhibit the metabolism of methanol and ethylene glycol.

Methanol and ethylene glycol intoxication is very rarely encountered in the United States. Approximately 6,800 to 7,800 cases are reported each year, reflecting about 2% to 3% of all the reported poisoning cases. The incidence is much higher in countries where people consume illicit alcohol that contains methanol. Ethylene glycol intoxication is clinically characterized by the presence of renal failure and envelope-shaped oxalate crystals in the urine.

Methanol intoxication commonly presents with ocular manifestations, neurologic damage, and metabolic derangements, leading to respiratory failure and death. Patients usually have papilledema on fundoscopic examination but this finding may be absent.

The toxic effects of methanol intoxication are mediated through its final metabolite, formic acid. Several studies have reported a correlation between the symptoms of poisoning or neurologic sequelae and the blood formic acid levels. Because the generation and accumulation of formic acid takes time, a latent period of about 12 to 24 h exists prior to the development of metabolic acidosis as well as signs and symptoms of intoxication. This latent period is further increased in patients with concomitant ethanol and methanol use, as ethanol inhibits the metabolism of the latter.

Few cases have been reported where there has been development of putaminal necrosis or hemorrhage secondary to methanol intoxication. The exact incidence rate of putaminal necrosis in patients with methanol intoxication as well as its exact mortality and morbidity rates remain unknown. The exact mechanism of putaminal damage in methanol intoxication remains unclear. It has been proposed that formic acid has a predilection to accumulate in higher concentration within the putamen and impair dopaminergic pathways. Another proposed mechanism suggests that putaminal necrosis results from decreased venous outflow through the veins of Rosenthal.

Some of the other known causes of putaminal necrosis include Wilson disease, anoxic strokes, striatal degeneration, Leigh disease, and Kearns-Sayre syndrome. Putaminal changes may also be seen in carbon monoxide inhalation, trichloroethane poisoning, acute cyanide intoxication, and hypoxic-ischemic injuries like drowning. Clinically, putaminal necrosis is characterized by the presence of mental status changes, disinhibited behavior, anosmia, memory impairments, and tremors. Delayed manifestations of putaminal necrosis include extrapyramidal signs and symptoms like rigidity, masked faces, tremors, and monotonous speech.

Treatment with fomepizole early in the course slows the rate of formic acid production, thereby preventing these potential toxicities. Hemodialysis helps to remove the accumulated formic acid, thereby preventing and/or reducing the severity of these potential toxicities. Therefore, once methanol intoxication is suspected, fomepizole along with hemodialysis should be administered immediately.

Clinical Course

The patient was reintubated for airway protection. She failed to show improvement in her mental status. Subsequently, tracheostomy and percutaneous gastric tube were placed, and she was transferred to a long-term rehabilitation facility.

Clinical Pearls

1. *Methanol and ethylene glycol intoxication are characterized by the presence of high-anion-gap metabolic acidosis and elevated serum osmolar gap.*
2. *Patients presenting 24 h after ingestion might only have high-anion-gap metabolic acidosis without any osmolar gap.*
3. *For patients suspected of having methanol intoxication, immediate administration of fomepizole blocks the conversion of methanol to formic acid and hemodialysis removes the acid already formed, thereby preventing the potential toxicities.*
4. *Putaminal necrosis and/or hemorrhage are well-established, but rare, late complications of methanol intoxication.*
5. *Patients that survive after an acute episode of putaminal necrosis develop extrapyramidal symptoms like rigidity, tremors, monotonous speech, and masked faces requiring therapy with levodopa.*

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Suggested Readings

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