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Short Communication

Black urine due to urobilinogen in a patient with alcoholic pellagra

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ABSTRACT

Objectives: Systemic exposure to drugs, chemicals and foods can cause abnormally colored urine. Food exposures are typically benign, but urine discoloration due to chemicals or drugs may indicate a potentially dangerous condition. Discolored urine can also be caused by medical problems. This brief report reviews the laboratory findings leading to lactic acidosis and elevated urine urobilinogen in an alcoholic patient with pellagra.

Design and methods: A 66-year-old male, found unconscious in his hotel room, was brought to the emergency department (ED). Upon arrival he had hypothermia, a diffuse rash and altered mental status. During ED evaluation, a urinary catheter was placed and demonstrated black urine. Medical history noted chronic alcoholism, malnutrition, and poor self-care.

Results: Evaluation in the hospital suggested that his rash and neurologic changes were a result of malnutrition and vitamin deficiency. A thorough biochemical workup demonstrated that elevated urobilinogen was likely causing the patient's black urine. Serum niacin concentration was undetectable. His dermatitis improved with multivitamins, thiamine, and niacin as well as topical steroids. His mental status returned to baseline and he was discharged to a skilled nursing facility following a brief hospital stay.

Conclusions: The patient's abnormal laboratory results were explained by his alcoholism and poor nutrition. Furthermore, urine color returned to normal with decreased concentration of urobilinogen, after vitamin supplementation and supportive medical care.

Introduction

A patient with black urine can represent a diagnostic challenge. Formulating an adequate differential diagnosis involves careful consideration of the causes and physiologic processes that lead to urine discoloration. There are many reasons why the body may form black discolored urine. Broadly, these include: a) drugs [1,2] b) endogenous substances such as urobilinogen [3], and c) pathologic conditions such as hemolysis [4,5] and alkaptonuria [6]. Intoxication from a widely used disinfectant, cresol has also been reported to cause black urine [7–9].

Case report

A 66-year-old male with a past medical history of emphysema, alcohol abuse, diffuse rash, substance abuse, unspecified liver disease, and previous suicide attempts was found unresponsive in his hotel room. On arrival in the ED, the patient was awake and looking around but was nonverbal and not following commands. He was also noted to have diffusely dry, excoriated skin with patchy areas of erythema, lichenification and fissures. He had a core temperature of 28.2 °C (82.8 °F). His caregivers stated that the patient was functionally debilitated and it was not uncommon for the patient to go multiple days without eating a meal. They also noted that the patient was at his baseline mental status and able to transfer between bed and commode a few days before his hospital presentation. While in the ED, a urinary catheter was placed and the urine recovered was noted to be black. The urine was sufficiently dark that the ED physician contacted the lab to see if it could be analyzed for iodine.

Discussion

Biochemically, (Table 1) the patient presented with an anion gap lactic acidosis and hyperosmolality. The plasma anion gap was minimally elevated 22 (reference 10–20 mmol/L) and the hyperosmolality could be explained using a common formula of 2 × sodium + (glucose / 18) + (urea nitrogen / 2.8) + (ethanol / 4.6) = 354 mOsm/kg. This calculated osmolality matched with the measured osmolality of 358 mOsm/kg, which helped rule out other alcohols (such as methanol or ethylene

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Table 1
Selected laboratory results and corresponding reference ranges. Abnormal results are shaded.

Test	Patient	Reference range	Test	Patient	Reference range
Chemistry			Creatine kinase, U/L	102	0–175
Sodium, mEq/L	149	136–145	TSH, uIU/mL	1.9	0.3–4.2
Potassium, mEq/L	4.3	3.5–5.1	Venous blood gases		
Chloride, mEq/L	108	98–107	pH	7.26	7.33–7.40
Bicarbonate, mEq/L	23	22–29	Bicarbonate, mEq/L	21	25–30
Urea nitrogen, mg/dL	13	6–20	pCO_2, mm Hg	37	40–52
Creatinine, mg/dL	0.8	0.7–1.2	Hematology		
GFR, mL/min	>60		Hemoglobin, g/dL	10.5	13.7–17.5
Glucose, mg/dL	145	75–115	Hematocrit, %	31	40–50
Calcium, mg/dL	7.2	8.6–10.5	Haptoglobin, mg/dL	91	30–200
Lactate, mg/dL	106.2	4.5–19.8	Platelet count, $\times 10^9$/L	63	140–370
Alkaline phosphatase, U/L	467	40–129	Urinalysis		
Alanine aminotransferase, U/L	54	0–41	Color	Black	Yellow
Aspartate aminotransferase, U/L	156	0–40	Appearance	Clear	Clear
Conjugated bilirubin, mg/dL	1.6	<0.2	Specific gravity	1.023	1.002–1.030
Total bilirubin, mg/dL	2.4	<1.2	pH	6	5–8
Albumin, g/dL	1.7	3.5–5.2	Protein	1+	Negative
Total protein, g/dL	5.7	6.0–8.0	Bilirubin	Moderate	Negative
Osmolality, mOsm/kg	358	275–295	Blood	Negative	Negative
Alcohol, mg/dL	197	None	Urobilinogen	>8	(0.2–1 EU/dL)
Magnesium, mg/dL	1.9	1.7–2.6			

glycol) which are in the differential diagnosis of a patient with altered mental status and an elevated anion gap metabolic acidosis with hyperosmolality. The patient also had biochemical findings consistent with an insult to his liver, demonstrated by elevations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase. The AST/ALT ratio of 2.9 is consistent with the patient's history of chronic alcoholism. Another notable chemical finding was the low albumin in the presence of a nearly normal total protein. Subtracting albumin from the total protein leaves 4.0 g/dL of globulins and an albumin to globulin ratio of 0.43 consistent with polyclonal hypergammaglobulinemia commonly seen in alcoholics [10]. The hypocalcemia can also be explained by the low serum albumin. When corrected [corrected calcium, mg/dL = total calcium (mg/dL) + 0.8 × (4 − serum albumin (g/dL))] for the amount of albumin present, the calcium (9.0 mg/dL) appears normal.

The clinicians initially suspected that the patient might have ingested iodine and contacted the lab because the patient had altered mental status and had intense black urine that stained the collection containers. No elevation of iodine was detected when analyzed by inductively-coupled plasma mass spectrometry (ICP-MS). Subsequent urinalysis revealed concentrations of urobilinogen that exceeded the linear range of our assay (>8 EU/dL). The urine was also analyzed by liquid chromatography-time of flight mass spectrometry (LC-TOF) to rule out possible intoxication due to 61 frequently encountered drugs and cresol. LC-TOF analysis was negative for these compounds but did confirm a compound consistent with urobilinogen with a protonated accurate mass of 593.3339 Da.

Elevated urobilinogen was the likely explanation for the dark coloration of urine, but why was the concentration of urobilinogen so elevated? In the setting of anemia, elevated urine urobilinogen can be caused by intravascular hemolysis. This patient was anemic, but his unconjugated bilirubin was not elevated and the normal haptoglobin helped rule out intravascular hemolysis. Given the cachectic appearance of the patient, history of malnutrition, altered mental status, and persistent rash, a vitamin deficiency was also suspected. Ultimately, alcoholism was responsible for the major clinical and biochemical findings in this case: lactic acidosis, liver dysfunction, and malnutrition.

Lactic acidosis

Lactic acidosis is generally divided into 2 types. Type A is due to tissue hypoxia and type B is due to reasons other than tissue hypoxia. Ethanol can cause type B lactic acidosis. Ethanol metabolism leads to the generation of excess NADH (Fig. 1; top). In this case NADH drives the conversion of pyruvic acid to lactic acid [11]. Lactic acid production was a significant feature in this patient's presentation, as his lactate concentration was 106.2 mg/dL, over five times the upper reference range. Without evidence of tissue hypoxia on diagnostic workup, the etiology of lactic acidosis in this case is likely related to chronic alcoholism causing both an excessive body burden of ethanol derived NADH as well as a diminished hepatic lactate clearance.

Liver dysfunction

Red cell catabolism and subsequent heme degradation by the endoplasmic reticulum release bilirubin into the circulation. Albumin transports bilirubin to hepatocytes where it is converted into water soluble bilirubin di-glucuronide (conjugated) and excreted into bile. Intestinal bacteria de-conjugate bilirubin so it can be reabsorbed or be further metabolized into urobilinogen (Fig. 1; bottom). Some of the urobilinogen is also reabsorbed from the gut and enters the portal blood. In healthy subjects the majority of reabsorbed urobilinogen is cleared by the liver [12–14]. Decreased clearance of urobilinogen by a diseased liver can lead to elevated urobilinogen. This patient is a chronic alcoholic and his laboratory results are consistent with decreased liver function (e.g. low albumin), and likely impaired hepatic urobilinogen clearance. The remaining urobilinogen enters the general circulation, is transported to the kidney, and is ultimately excreted in the urine.

Malnutrition

The leading cause of pellagra is the deficiency of niacin (vitamin B_3) and tryptophan due to malnutrition. Pellagra is clinically manifested by diarrhea, dermatitis, and dementia. The patient was a chronic alcoholic and alcoholism is one of reasons often associated with malnutrition [15]. The initial clinical exam of this patient noted an overall cachectic appearance, suggestive of malnutrition. The patient's niacin concentration was undetectable (reference range 0.5–8.45 μg/mL). The patient was diagnosed with pellagra due to niacin deficiency and the constellation of frequent loose stools, diffuse skin rash, and altered mental status.

Case resolution

The patient underwent computed tomography studies of the head, abdomen and pelvis which were remarkable for nonspecific colonic

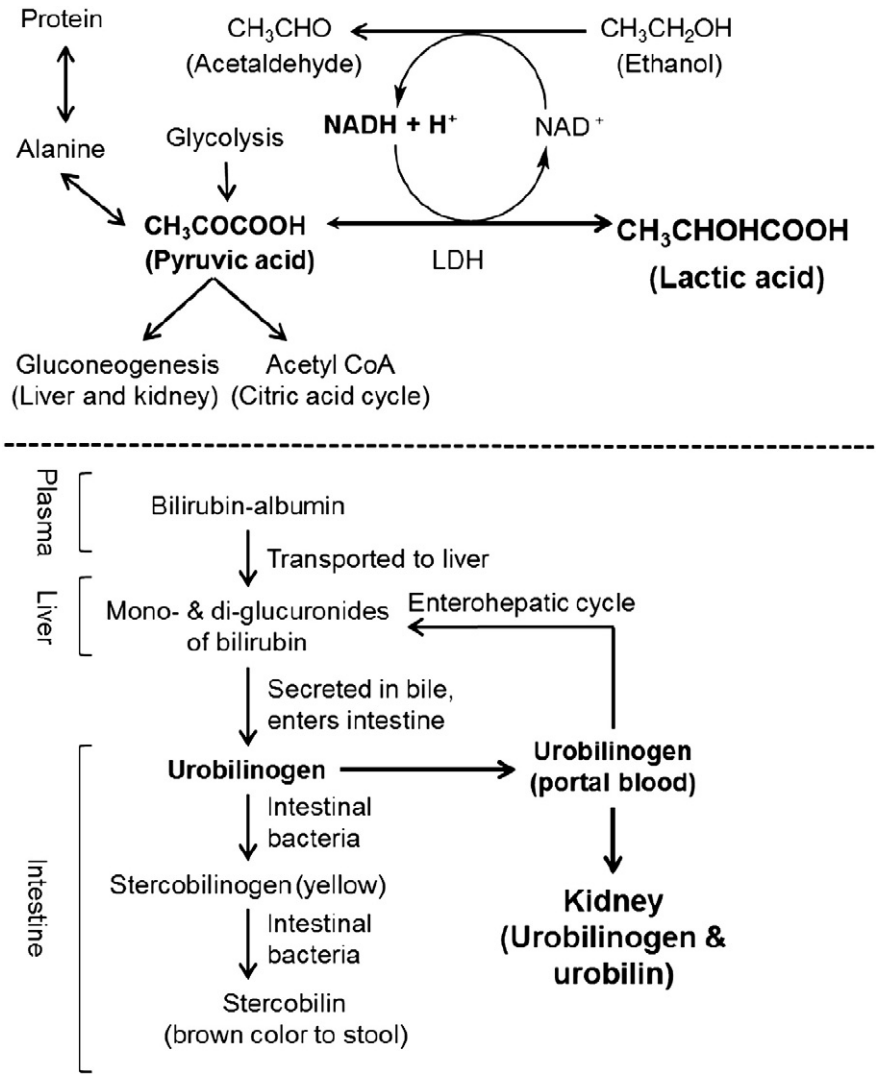

Fig. 1. Top (lactic acid formation): increased amount of NADH in the presence of ethanol favors the conversion of pyruvic to lactic acid (in bold). Bottom (bilirubin metabolism): decreased hepatic clearance could lead to increased concentration of urobilinogen in urine (in bold).

thickening and fatty liver infiltration. An ultrasound of the abdomen demonstrated fatty liver infiltration, as well as a small amount of ascites but no biliary abnormalities were noted. Chest radiograph demonstrated calcified pleural plaques suggestive of prior asbestos exposure but a lung mass was not appreciated. He was initially treated with broad-spectrum antibiotics for possible sepsis along with intravenous dextrose, thiamine, and folic acid supplementation. The antibiotics were discontinued after 2 days when the patient's blood and urine cultures did not demonstrate bacterial growth. His anion gap and lactic acidosis also improved with therapy. Hypothermia on presentation was treated with external warming measures, subsequently improved, and was felt to be related to environmental exposure and alcohol intoxication. His thyroid stimulating hormone was normal. Hypernatremia resolved with intravenous fluids and was felt to be due to dehydration. The workup for anemia was unrevealing of a specific cause and was attributed to chronic disease. Thrombocytopenia was likely from chronic alcoholism. Transaminase elevations were likely from chronic alcohol use and improved with fluid resuscitation and cessation of alcohol use. Dermatology consultation was obtained for the patient's skin abnormalities, which was diagnosed as possible seborrheic dermatitis, atopic dermatitis, or dermatitis from malnutrition and vitamin deficiency. His dermatitis improved significantly with multivitamin, thiamine, and niacin administration as well as topical steroid creams. His urine color returned to normal with decreased concentration (6 EU/dL) of urobilinogen. He was discharged to a skilled nursing facility for further care following a one week hospital stay.

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