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Case Report

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Lactic Acidosis and Electrolyte Disturbances Associated With Hypertriglyceridemia in an Adolescent Receiving Chemotherapy for Acute Lymphoblastic Lymphoma

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Abstract

Given the association of lactic acidosis with inadequate tissue perfusion and poor clinical outcomes, an aggressive investigation and alterations in supportive and therapeutic care are needed for patients with lactic acidosis. However, other etiologies of lactic acidosis may exist, including disorders of excessive production or inadequate clearance. Several of these fall under the category known as "type B" lactic acidosis. We present a 17-year-old female with acute lymphoblastic leukemia who was admitted to the pediatric intensive care unit (PICU) for evaluation of lactic acidosis and severe hyponatremia. Subsequent evaluation argued against pathologic etiologies of lactic acidosis, leading to the conclusion that the high lactic acid laboratory value was caused by hypertriglyceridemia.

Keywords: Lactic acidosis; Hyperlipidemia; Triglycerides; Hypertriglyceridemia; Asparaginase

Introduction

Lactate is a product of anaerobic metabolism that is produced in all body tissues and serves as a secondary marker of tissue hypoxia and cellular distress [1]. Lactate is produced under normal circumstances, but is metabolized in the liver through conversion to pyruvate, thereby maintaining homeostasis [2]. When lactate production exceeds consumption, it accumulates in the body, causing lactic acidosis. The accumulation of lactate in low flow states and sepsis correlates with morbidity and mortality, making it a useful serum marker to follow in the management of critically ill patients [2].

Lactic acidosis is classified into two main types: type A and type B. By far, the most common type of lactic acidosis is type A, which is secondary to tissue hypoxia and may present in conditions such as cardiogenic and hypovolemic shock, sepsis, and severe systemic hypoxemia [3]. Less commonly, lactic acidosis can occur in the absence of tissue hypoxia, known as type B lactic acidosis. This occurs through several mechanisms, including an increase in aerobic glycolysis secondary to β_2-adrenergic stimulation, hepatic dysfunction with decreased clearance, medications (metformin, epinephrine), total parenteral nutrition, thiamine deficiency, mitochondrial myopathy, and strenuous exercise [1, 2, 4]. Unlike type A lactic acidosis, type B is not associated with poor clinical outcomes.

Given the more common association of lactic acidosis with inadequate tissue perfusion and poor outcomes, a thorough diagnostic evaluation is indicated in patients with lactic acidosis. We present a 17-year-old adolescent female with acute lymphocytic leukemia (ALL) who was admitted to the pediatric intensive care unit (PICU) with lactic acidosis and hyponatremia. Without clinical or laboratory evidence of tissue hypoxia, the prevailing clinical evidence suggested that the high lactic acid was a misleading finding caused by hypertriglyceridemia, which resulted from asparaginase treatment.

Case Report

A 17-year-old female with high-risk B-cell ALL in complete remission and a past history of chronic pulmonary aspergillosis, hypertension, non-occlusive cerebral venous thrombosis, and abnormal uterine bleeding presented to oncology clinic during interim maintenance 2 (IM2) chemotherapy with 2 days of acute-on-chronic abdominal pain, vomiting, and poor

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Table 1. Home Medication Regimen

Sulfamethoxazole-trimethoprim
Posaconazole
Nifedipine
Mirtazapine
Scopolamine patch
Cyproheptadine
Enoxaparin subcutaneous
Medroxyprogesterone
Famotidine

appetite. Recent chemotherapy included day 41 IM2 with vincristine 1.5 mg/m^2 and methotrexate 75 mg/m^2 administered 3 days prior and calaspargase 2,500 IU/m^2 administered 23 days prior. Prior to IM2, the patient had received treatment as per standard Children's Oncology Group high risk protocol with induction, consolidation, interim maintenance 1, and delayed intensification, with initial treatment starting 1 year prior to this presentation. Home medications outside of chemotherapy are provided in Table 1. In the clinic, vital signs were normal except for an elevated heart rate (HR) of 148 beats per minute (bpm). Her physical examination was unremarkable except for a mildly distended abdomen with diffuse abdominal pain without guarding. A complete blood count (CBC) and a basic metabolic panel revealed a white blood cell count of 0.8 × 10^3/µL, an absolute neutrophil count of 0.4 × 10^3/µL, a platelet count of 38 × 10^3/µL, sodium of 117 mmol/L, chloride of 4 mmol/L, potassium of 3.3 mmol/L, carbon dioxide of 16 mmol/L, and triglycerides (TG) of 4,952 mg/dL. The decision was made to transfer the patient to the PICU for management of severe hyponatremia and high anion gap lactic acidosis. In the PICU on day of hospitalization 1 (DOH 1), a venous blood gas was remarkable for a lactate of 4.1 mmol/L with a pH of 7.47. Amylase and lipase were collected to rule out pancreatitis and were normal (37 and 106 U/L, respectively). Subsequent levels throughout the hospitalization remained within normal limits. Despite multiple attempts, the hemoglobin value remained unquantifiable on the CBC due to lipemic interference from hypertriglyceridemia. Due to high lactate level, persistent tachycardia, and the inability to obtain reliable hemoglobin values, a decision was made to transfuse a unit of red blood cells, which decreased the HR to 120 bpm. Fenofibrate, fish oil, and insulin with dextrose at 15% were started for the management of hypertriglyceridemia. On DOH 2, TG levels began to decrease, but other laboratory values remained significantly abnormal and variable (Table 2). An abdominal ultrasound was done to rule out abdominal pathology as the source of the elevated lactate; results were remarkable for fatty liver, but no other abnormalities were found. Her home nifedipine regimen was restarted for persistent hypertension (Table 1). On DOH 3, the patient was again persistently tachycardic with an HR of 140 - 150 bpm, with numerous inconsistent laboratory results that were attributed to the high TG levels. An echocardiogram and electrocardiogram were performed, both yielding normal results. Nephrology was consulted and felt that hyponatremia

Table 2. Trend of Laboratories During Hospital Admission

Laboratory value	DOH 1	DOH 2	DOH 3	DOH 4	DOH 5	DOH 6	DOH 7	DOH 8	DOH 9	Two weeks after discharge	Reference range
Sodium	117 - 124	114 - 130	116 - 130	117 - 125	111 - 114	112 - 120	117 - 123	125 - 130	131 - 135	139	135 - 145 mmol/L
Chloride	84 - 88	85	88	88	79 - 82	80 - 87	83 - 87	9 - 94	97 - 99	103	98 - 110 mmol/L
Carbon dioxide	13 - 16	17	16	17 - 18	18 - 19	19 - 15	2 - 24	24 - 25	24 - 27	25	21 - 30 mmol/L
Triglycerides	4,952	3,490	2,540	2,601	1,798	1,632	-	-	-	372	< 90 mmol/L
Lactate	4.3 - 6.6	6.2 - 8	4.4 - 5.5	6.6	4.5	4	3.8	2.9	3.5	-	0.5 - 2.2 mmol/L

The patient was in the PICU on DOH 1-5 and then the patient hematology/oncology inpatient ward on DOH 6-9. DOH: day of hospitalization; PICU: pediatric intensive care unit.

was likely multifactorial, related to hypovolemic hyponatremia as well as pseudo-hyponatremia secondary to hypertriglyceridemia. A trial of oral sodium chloride supplementation was attempted unsuccessfully secondary to emesis. Three milliliters per kilogram of 3% NaCl was administered without the expected increase in the serum sodium value. Intravenous fluids were increased to 1.5 times maintenance and the patient was allowed to have a clear liquid diet as tolerated. The patient continued to have elevated lactate levels and an HR of 130 - 140 bpm with normal mental status and no clinical signs of hypoperfusion. The insulin and glucose infusions were discontinued, but fish oil and fenofibrate were continued. Due to her consistently stable clinical status despite inconsistent laboratory values, the patient was transferred to the oncology inpatient ward. On DOH 5, severe hyponatremia persisted despite down trending TG levels. A differential diagnosis of syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to chemotherapy, cerebral salt wasting, and adrenal insufficiency were considered as possible etiologies. Ultimately, SIADH was felt to be most likely at this time point, and fluid restriction was initiated along with 2,000 mg of sodium chloride every 4 h by mouth. On DOH 6, sodium levels began to improve, but lactate levels remained inconsistent. Sodium chloride administration was decreased to every 6 h. On DOH 7, a random cortisol level was 26.6 µg/dL, ruling out adrenal insufficiency. Sodium and TG levels continued to improve, but lactate and serum bicarbonate levels remained inconsistent. On DOH 8, the sodium level had increased to 135 mmol/L with a serum bicarbonate of 27 mmol/L. Based on the stable clinical status of the patient and correction of the hyponatremia and metabolic acidosis, the decision was made to discharge her home. However, on the day of discharge, lactate levels remained elevated at 3.5 mmol/L. Sodium levels stabilized following discharge and remained normal as sodium supplements were weaned. Two weeks after discharge, the patient returned to the hospital to begin a cycle of blinatumomab; routine laboratories were checked including TG and values remained stable (Table 2).

Discussion

ALL is the most common cancer in the pediatric population, accounting for over a quarter of all malignancies in children under 19 years old [5]. Asparaginase, a component of ALL chemotherapy treatment regimens, reduces the serum concentration of asparagine, depriving the leukemic blast cells of this amino acid, thereby affecting the synthesis of proteins which results in cellular death [6]. Despite being an effective agent in the treatment of ALL, it is known to have several potential adverse effects including hypersensitivity reactions, hyperglycemia, pancreatitis, thrombosis, encephalopathy, myelosuppression, hepatotoxicity, and hypertriglyceridemia [6, 7].

In general, hypertriglyceridemia can be defined as a fasting serum TG level ≥ 150 mg/dL [8]. Approximately 67% of the patients receiving asparaginase experience transient elevations in TG levels [9]. Management generally relies on non-pharmacological modalities including a diet restricted in lipids and carbohydrates. Therapeutic interventions may include medications (fibrates, statins, niacin and insulin) or apheresis [8, 9].

Our patient was originally admitted for aberrant laboratory values (severe hyponatremia and hypertriglyceridemia) and abdominal pain. In the PICU, she was incidentally found to have anion gap metabolic acidosis with an elevated lactic acid. We postulated that at least some component of the hyponatremia was related to the hypertriglyceridemia. In normal circumstances, blood is composed of 93% plasma water and 7% proteins, and the calculation of sodium is made based on this assumption. In the presence of hyperlipidemia, the proportion of plasma water decreases, provoking a false interpretation of the sodium plasma concentration. However, this does not affect plasma osmolality, and thus is designated as pseudohyponatremia [10]. Other possible contributing factors to the hyponatremia on initial presentation and during subsequent hospitalization included hypovolemic hyponatremia, given the clinical presentation with vomiting and poor oral intake or SIADH since vincristine was part of the chemotherapeutic regimen and has been associated with SIADH [11].

One of the more unusual findings in this case was the unexplained lactic acidosis. With type A lactic acidosis in low flow states, lactate levels have a direct relationship with morbidity and mortality [2]. However, lactate is not exclusively due to cellular hypoperfusion, as it also may be related to type B lactic acidosis. This occurs when the amount of pyruvate present in the blood exceeds the capacity of pyruvate dehydrogenase to produce acetyl-CoA, which then enters the Krebs cycle. When the metabolic capacity of pyruvate dehydrogenase is exceeded, pyruvate is metabolized by lactate dehydrogenase to lactic acid [1, 4]. Type B lactic acidosis can also occur in the presence of medications that induce glycolysis, in hyperglycemic states, and with hepatic dysfunction. Another less common cause for elevated lactate in the absence of hypoperfusion is thiamine deficiency. This vitamin serves as a cofactor for pyruvate dehydrogenase [4]. It is not uncommon for patients receiving chemotherapy to develop malnutrition and vitamin deficiencies [12]. While we did not measure her thiamine level during the hospitalization, she clinically did not have other clinical manifestations of thiamine deficiency (encephalopathy, hemodynamic concerns), therefore making this lower in the differential diagnosis [13].

The primary metabolic concerns noted in our patient were the wide anion gap acidosis (low serum bicarbonate) and the high lactate levels. The former is easier to explain and has been reported previously in association with hypertriglyceridemia, due to a factitiously low bicarbonate [14-16]. This can occur by different mechanisms including volume displacement and disruption of spectrophotometry. As previously mentioned, volume displacement in the setting of hypertriglyceridemia can cause errors in lab results secondary to reduction of plasma in relation to lipids and proteins [10]. In addition, as bicarbonate is measured by spectrophotometry; elevated TG can disrupt the light absorption causing a factiously low bicarbonate level [16]. What is more difficult to explain, and remains somewhat speculative, is the elevated lactic acid levels noted in our patient. Our patient developed hypertriglyceridemia secondary to impaired insulin production and release related to the adverse effects of asparaginase on pancreatic β cells [17]. These TG would be metabolized through β-oxidation and subsequent entry into the Krebs cycle

with increased production of acetyl-CoA. Excessive amounts of acetyl-CoA can exceed the enzymatic capacity of the Krebs cycle, leading to inability of pyruvate to enter into the cycle and its subsequent shunting to lactate production following metabolism by lactate dehydrogenase [18]. Although TG do not directly produce lactate, they may impede pyruvate produced in glycolysis from entering the Krebs cycle, leading to its conversion into lactate [19]. To our knowledge, this clinical finding of elevated lactate in the setting of severe hypertriglyceridemia has not been previously reported.

As an isolated case report, there are specific limitations that must be noted beyond the anecdotal nature of what we found. Despite a downward trend of the hypertriglyceridemia, there was a persistent mild elevation of the lactic acid level. As the hypertriglyceridemia was resolving, daily follow-up of the TG level was not documented after the patient was transferred out of the PICU. As this is the first anecdotal report regarding the association of elevated lactic acid with hypertriglyceridemia, additional work is required to firmly prove a causal relationship.

Conclusion

Lactic acidosis can be a strong indicator of both morbidity and mortality, when related to tissue hypoperfusion. Identification of the etiology of lactic acidosis allows for effective treatment and therapeutic interventions. Although several of the metabolic derangements seen in our patient may have been related to the impact of high TG levels on laboratory assays, a biochemical mechanism may have been responsible for the high lactate levels. We postulate that high TG levels led to increased production of acetyl-CoA, which prevented entry of pyruvate into the Krebs cycle, leading to impaired pyruvate metabolism and increased lactate production. Clinicians should recognize that hyperlactatemia can arise in situations unrelated to hypoperfusion. Secondarily, high TG levels can falsely lower bicarbonate and sodium measurements.

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Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained for anesthetic care and the use of de-identified information for publication.

Author Contributions

JC: preparation of initial, subsequent, and final drafts, and patient care; JDT: concept, writing, and review of all drafts; MD, NS, and SIC: care of the patient and review of final draft.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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