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A Case of Severe Type B Lactic Acidosis in a Patient with Acute Lymphoblastic Leukemia

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Abstract

The development of type B lactic acidosis related to hematologic malignancies is a rare phenomenon. The exact mechanism is not known but can result in death if not recognized and corrected. The mainstay of therapy remains systemic cancer-directed therapy to treat the underlying disease although intravenous bicarbonate and renal replacement therapy have been employed at times for acute treatment of severe lactic acidosis as a bridge until chemotherapy can be initiated. However, these therapies do not appear to have a long-term effect. In this case report, we present a 75 year-old male with acute lymphoblastic leukemia who was admitted to the hematology/oncology service after routine labs drawn in clinic revealed a lactate dehydrogenase (LDH) level of 4554 U/L thought to be due to severe type B lactic acidosis portending poor prognosis. Prompt diagnosis and treatment of this rare complication of hematologic malignancies is critical in trying to prevent poor outcomes as much as possible.

Keywords: *Severe Type B Lactic Acidosis; Acute Lymphoblastic Leukemia; Hematologic Malignancies; Lactate Dehydrogenase (LDH)*

Abbreviations: *LDH: Lactate Dehydrogenase; AML-M6b: Pure Erythroid Leukemia; ALL: Acute Lymphoblastic Leukemia; TNFα: Tumor Necrosis Factor Alpha; NRTIs: Nucleoside Reverse Transcriptase Inhibitors; HIV: Human Immunodeficiency Virus; MG: Milligrams; ML: Milliliters; MIN: Minute*

Introduction

Type B lactic acidosis is a distinct form of metabolic acidosis characterized by low blood pH (normal=7.35-7.45) and the accumulation of lactate in the blood (blood concentration greater than or equal to 5 mmol/L) [1]. It is of particular interest because it is a rare and often lethal complication of hematologic malignancies. Its exact mechanism is not well understood although several possible mechanisms have been proposed as discussed below in this case report. There appears to be some association with common diseases (i.e., diabetes), drugs, toxins, inborn errors in metabolism, and hereditary/miscellaneous disorders. In comparison, type A lactic acidosis which is much more common and has been more extensively studied usually results due to lack of oxygen from significant tissue hypoperfusion or acute severe hypoxemia. Impaired cellular respiration forces cells to metabolize glucose anaerobically and thus results in increased production of lactate [2,3]. In this case report, we present a 75 year-old male with acute lymphoblastic leukemia who was admitted to the hematology/oncology service after routine labs drawn in clinic revealed an LDH of 4554 U/L without other evidence of tumor lysis syndrome. His overall clinical presentation was felt to be most consistent with severe type B lactic acidosis portending a poor prognosis.

Case Presentation

Our patient is a 75 year-old male with acute lymphoblastic leukemia on palliative chemotherapy who was admitted to the hematology/oncology service after routine labs drawn in clinic revealed an LDH of 4554 U/L. At the time of presentation, he endorsed increased generalized weakness and fatigue over the past 2-3 weeks. He also reported decreased oral intake due to mouth pain for a couple of days prior to admission. At baseline, he had poor functional status and spent most of his time in bed. He had also been noted to have intermittent disorientation since his last cranial radiation treatment 5 months prior to admission.

In the emergency department, his vital signs were within normal limits. Physical examination was notable for petechiae on the palette and oropharyngeal thrush. There was no apparent lymphadenopathy and neurological examination was unremarkable. Labs were significant for thrombocytopenia (platelet count=26,000/μL), anion gap elevated to 25, mild hypercalcemia, mild transaminitis, lactate increased to 14.2 mmol/L, LDH significantly increased to 4554 U/L, and trace ketones on urinalysis. Electrocardiogram showed no acute ischemic changes. Posteroanterior and lateral chest x-rays were within normal limits.

Regarding his oncology history, the patient was initially diagnosed with AML-M6b via bone marrow biopsy 3.5 years prior to admission after initial presentation to his primary care physician for evaluation of extensive abdominal and extremity bruising. He underwent 7+3 induction chemotherapy with cytarabine and daunorubicin which was complicated by lower extremity edema and ascites that resolved without intervention. His blood counts improved to baseline post-chemotherapy and no further chemotherapy was pursued due to risk of neurotoxicity in an elderly patient. He was then in remission for nearly 1 year when he developed dyspepsia and dysphagia with solids and left eye ptosis related to 3rd nerve palsy.

Gastric biopsies were consistent with ALL. Lumbar puncture and bone marrow biopsy confirmed ALL with central nervous system involvement after which ECOG E2993 Protocol: Phase I (vincristine/prednisone, intrathecal methotrexate, and daunorubicin) was initiated but was complicated by profound neutropenia and neuropathy. Phase II (cyclophosphamide, cytarabine, and 6-mercaptopurine) was initiated about a month later followed by 1 cycle of consolidation chemotherapy with cytarabine/etoposide but this was complicated by herpes zoster scalp infection. About 4 months later, maintenance therapy (prednisone, mercaptopurine, methotrexate, and vincristine) was initiated but patient subsequently developed double vision thought to be secondary to 6th nerve palsy after about 3 months of treatment. Lumbar puncture confirmed recurrence of malignant cells in the cerebrospinal fluid despite treatment with intrathecal methotrexate prompting hydrocortisone to be added. Bone marrow biopsy done about 3 months later confirmed systemic relapse and cerebrospinal fluid showed persistence of malignant cells for which cranial radiation therapy was started. The patient was then hospitalized 2 months later with sepsis after administration of vincristine/prednisone and was noted to have changes in mental status characterized as increased boredom and fatigue. About a month later, he was referred to hospice care but did not enroll. Increasing LDH to 2008 U/L was noted 2 months later at which time vincristine/prednisone were discontinued due to thrombocytopenia requiring platelet transfusions. Fludarabine was initiated about a month later without adverse effect. LDH remained elevated but stable at the time and uric acid remained within normal limits.

Upon arrival to the hematology/oncology floor, patient was continued on intravenous fluids (normal saline). His extreme elevation in LDH with an upward trend over the past few months was thought to be due to progression of ALL. The reason for acute elevation to 4554 U/L on admission remained unclear. Tumor lysis syndrome was not felt to be contributing given lack of electrolyte abnormalities and uric acid found to be within normal limits. LDH improved to 2551 U/L with administration of normal saline for a few days prior to discharge suggesting a component of hypovolemia. Patient was discharged with plan for close monitoring of his labs in the outpatient setting. Salvage chemotherapy with vincristine and prednisone was started shortly after discharge but was discontinued after one cycle due to poor functional status and goals of care were shifted to comfort-focused care within a couple of weeks.

Profound lactic acidosis with gradually increasing anion gap in correlation with increasing LDH was thought to be secondary to type B lactic acidosis related to progressive ALL although the pathophysiologic mechanism for this is unknown. It was felt that type A lactic acidosis was clinically unlikely as patient remained without abdominal pain, hematochezia, signs or symptoms of ischemic disease, and no acute elevation in lactate or acidemia. The gradual rise of lactate and compensated pH as seen in this patient is not typical for type A lactic acidosis. Given this clinical scenario, it was felt that imaging of the abdomen was not indicated to rule out an ischemic process. Drug-induced lactic acidosis was also considered as patient reported compliance with metformin 500 mg by mouth daily although there was low suspicion that this may be the cause of lactic acidosis given stable renal function (glomerular filtration rate = 89 mL/min). It was, however, discontinued at the time of discharge in case it was contributing. As G6PD deficiency can also elicit type B lactic acidosis, atovaquone for Pneumocystis carinii pneumonia prophylaxis was discontinued although there was low suspicion for this as the cause of type B lactic acidosis given no prior documentation of G6PD deficiency and higher suspicion for other causes i.e., progression of ALL.

Overall, it was felt that the patient had advanced ALL with poorprognosis which likely led to his poor oral intake, fatigue, lethargy, and type B lactic acidosis. Emphasis was placed on hospice care and palliative efforts on an outpatient basis with the hope that he might respond to salvage chemotherapy.

Discussion

The development of lactic acidosis associated with hematologic malignancy is rare but confers very poor prognosis. Type B lactic acidosis in malignancy was first reported in an acute leukemia patient in 1963 [4]. Another case was reported in Korea in 1999 in a patient with leukemia transformed from lymphoma [5]. In 2007, a case of type B lactic acidosis associated with thiamine deficiency was reported [6]. Approximately 67 total cases have been identified via review of literature [7]. Two more recent cases of ALL complicated by lactic acidosis were reported in 2010 in Japan [3] and Korea [8]. It is unfortunate that the pathophysiologic process is poorly understood and there is still little evidence to support various treatment options. The data comes from case reports and case series of the few documented cases. The cause of type B lactic acidosis is likely multifactorial. There is some suggestion that its development is related to liver and/or kidney dysfunction, tumor cell overexpression of certain glycolytic enzymes and mitochondrial dysfunction, overexpression of TNF-α which results in reduced activity of pyruvate dehydrogenase, thiamine deficiency, and tumor lysis syndrome [7]. Liver and kidney dysfunction whether they be from tumor infiltration, ischemic damage, or other causes are thought to be two processes that contribute to the development of type B lactic acidosis as lactate is the end product of anaerobic metabolism and is converted to pyruvate and subsequently glucose by both the liver (90%) and kidneys (10%) [9] via glycolysis. However, many patients with kidney and liver dysfunction do not develop severe lactic acidosis which suggests that there is likely a more complex process or processes responsible for the development of severe lactic acidosis [7].

Another proposed mechanism relates to tumor cell overexpression of certain glycolytic enzymes and mitochondrial dysfunction [10-11]. Some tumor cells overexpress insulin-like growth factor-I and hexokinase which results in high rates of glycolysis and higher glucose levels, allowing for more rapid proliferation of cells. Despite the presence of oxygen, cancer cells often utilize anaerobic metabolism which results in significant production of lactate [10]. In addition, the presence of dense compressing tumor mass or leukemic microemboli can impair tissue perfusion and cause ischemia which results in increased anaerobic glycolysis [12].

TNFα may play a role in the development of type B lactic acidosis. The thought is that it has multiple paracrine actions on tumor cells and affects mitochondrial function. Specifically, TNFα causes a reduction in the activity of pyruvate dehydrogenase and inhibits the cytochrome-dependent electron transport system which results in increased lactate levels in addition to having systemic effects that alter hepatic glucose metabolism [13]. However, hyperlactic acidemia itself has been shown to increase transcription of the gene that encodes TNFα *in vitro* [14]. Studies have shown decrease in elevated TNFα levels after treatment of newly diagnosed patients with leukemia and non-Hodgkin lymphoma with chemotherapy [15]. It is unclear whether increased TNFα production reflects the process of malignant disease or the host's defense against it as ongoing cell proliferation itself can result in both elevated lactate and TNFα levels [14].

Thiamine deficiency is another possible mechanism that may trigger the development of type B lactic acidosis as thiamine is an important cofactor in the pyruvate dehydrogenase complex. Thiamine is necessary for the conversion of pyruvate into acetyl coenzyme A via pyruvate dehydrogenase. Hindrance of this pathway results in anaerobic metabolism and thereby results in production of lactate. This phenomenon has been reported in patients on total parenteral nutrition without vitamin supplementation although some of these patients also had malignancy. The acidosis in this situation was successfully reversed via addition of thiamine to the alimentation solution [16]. Furthermore, administration of methotrexate in chemotherapy regimens can result in the development of type B lactic acidosis because it competes with thiamine transport systems and results in inhibition of pyruvate dehydrogenase and initiation of anaerobic metabolism as described above [10,17]. Nucleoside reverse transcriptase inhibitors (NRTIs) used in the treatment of HIV have also been associated with the development of type B lactic acidosis due to mitochondrial dysfunction with aberrant glycolytic processes. Thiamine and riboflavin have been used to successfully treat this complication which suggests that vitamin deficiencies may be an important cofactor in the development of type B lactic acidosis in HIV patients [18-21].

Finally, tumor lysis syndrome has been attributed to the development of type B lactic acidosis as well. The thought is that apoptosis of tumor cells causes a loss in mitochondrial membrane potential which results in loss of mitochondrial function and leads to compensatory glycolysis with lactate formation and acidosis [22].

In the few cases of type B lactic acidosis that have been identified, it appears that many of the patients who developed this phenomenon had bulky disease or large tumor burden. This suggests that these patients may have the highest risk for development of type B lactic acidosis. Many also had hepatic and renal involvement [7]. While lactic acidosis

is infrequently encountered in malignancies (although when it does occur it is most often associated with acute leukemias and high-grade lymphomas), it portends an extremely poor prognosis when it presents and therefore should be considered an oncologic emergency. Review of literature on type B lactic acidosis reveals that many cases had concomitant sepsis, anemia, surgical procedures, abnormal vital signs, or at least one vital sign indicative of systemic inflammatory response so it is difficult to discern how many of these cases were due to lymphoma or leukemia-associated lactic acidosis alone [2].

The best treatment for patients with hematologic malignancies who develop type B lactic acidosis is unclear at this time. Initiation of aggressive chemotherapy has been effective in a small number of patients. It is the only treatment modality that has consistently led to remission. Thus, treatment of the primary condition (i.e., cancer-directed therapy for leukemia/lymphoma) remains the mainstay of therapy [8]. The resolution of lactic acidosis occurred in 6 out of 7 cases that responded to chemotherapy of the 29 cases reviewed by Chan *et al*. The lactic acidosis resolved in 5 of these 6 cases within 15 hours to 3 days and in the remaining case resolution was noted weeks after chemotherapy was introduced but within 2 days after salvage chemotherapy was initiated [2].

Until chemotherapy takes effect to treat the underlying malignancy, both intravenous bicarbonate and hemodialysis have been used to control lactic acidosis although its use is controversial. Since severe acidosis can cause respiratory fatigue and hemodynamic instability, intravenous bicarbonate is often given to reverse the lactic acidosis. However, there are potential severe side effects to this therapy including hypervolemia, hypernatremia, and even initial increase in lactic acid production [23-24]. The postulated mechanism for this is that decreased oxygen delivery results in reduced PaO_2 [25] and increased affinity of O_2 to hemoglobin results from the increase in systemic pH due to intravenous bicarbonate infusion [26]. Of these same 29 cases reviewed by Chan *et al*., 20 received intravenous bicarbonate to counter lactic acidosis. While only 2 of these patients received bicarbonate without adjuvant chemotherapy, both did not survive more than days. Of the 7 patients who went into remission, 6 of them had received intravenous bicarbonate. There is limited data available regarding use of intravenous bicarbonate as it has not been formally studied [2]. In addition, renal replacement therapy (hemodialysis, peritoneal dialysis, hemofiltration) in such cases of malignancy-related lactic acidosis has been used in a few instances as a bridge until chemotherapy can be initiated to treat the underlying cause [27]. However, 2 of 3 such reported cases died within 10 days of initiation of renal replacement therapy so its benefit is unclear. It appears that prompt diagnosis and early treatment of the underlying malignancy is the only way to achieve complete resolution of lactic acidosis in malignancy-related type B lactic acidosis [2].

In our patient, it is likely that his elevated LDH and type B lactic acidosis were due to progression of his refractory acute lymphoblastic leukemia. Other factors that could have contributed to its development include liver dysfunction as his liver function tests were notable for a hepatotoxic pattern without prior history of liver disease. He was not treated with intravenous bicarbonate, thiamine, or renal replacement therapy because he remained asymptomatic despite such extreme elevations in LDH and severe lactic acidosis. Rather, he was started on salvage chemotherapy (vincristine and prednisone) to treat the underlying cause which was felt to be progression of his ALL. However, this was stopped after one cycle and goals of care were shifted to comfort-focused care within weeks after discharge due to progressive failure to thrive and poor performance status.

Conclusion

Overall, type B lactic acidosis appears to be a rare but severe and often lethal complication of hematologic malignancies. The exact pathophysiology that governs its development still remains unclear although it appears to be multifactorial with a number of possible mechanisms postulated to describe its development as discussed above. Although rare, it is imperative that physicians be aware it can manifest at the time of initial diagnosis or in the setting of recurrence/advanced malignancy. The mainstay of therapy remains prompt treatment of the underlying disease with chemotherapy as this has been the only therapy found to be effective in terms of long-term resolution of the lactic acidosis and remission of the hematologic malignancy. A few cases have been noted to reach remission but the majority of cases have been fatal. For this reason, further investigation regarding the pathophysiology of type B lactic acidosis in hematologic malignancies is critical. In addition, early diagnosis and prompt treatment is imperative to prevent poor outcomes.

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