



CASE REPORT

Type B Lactic Acidosis Associated with T - Cell Acute Lymphoblastic Leukemia: A Pediatric Case Study

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Abstract

Background: Aerobic glycolysis or Warburg effect (WE) is a common cause of hyperlactatemia in adults with cancer, uncommonly seen in the pediatric population. We describe an unusual case of a teenager with lactic acidosis as the presenting lab abnormality with no other abnormality suggestive of an oncologic process, who was later diagnosed with T-cell acute lymphoblastic leukemia (ALL).

Case description: A 17-year-old previously healthy male presents with five days of vomiting, poor PO intake, body aches and headaches. Initial laboratory and diagnostic evaluations were significant for anion gap metabolic acidosis secondary to hyperlactatemia, transaminitis, elevated lipase, leukocytosis with mild bandemia and a CT scan of the abdomen concerning for changes consistent with infection. Due to worsening lactate on the pediatric floor despite fluid resuscitation and empiric antibiotics, the patient was transferred to the pediatric ICU (PICU). The lactate level at the time was 13 meq/l with a pH of 7.13. Serial inflammatory markers were low with negative blood and urine cultures. The urine drug screen was negative. The patient continued acetate-containing fluids, which improved the acidosis; however, hyperlactatemia remained. The lactate level peaked at 18 meq/L. The patient was felt to have an unknown etiology of lactic acidosis, which was concerning for a life-threatening process.

Given the abnormal CT scan and several case reports in adults suggestive of hyperlactatemia in malignancy, the decision was made to obtain a CT scan of the chest to look for a mass. CT scan showed a heterogeneous mass in the anterior mediastinum. Biopsy confirmed the diagnosis of T-cell ALL. A follow up PET scan revealed metastatic disease throughout the head and neck. Chemotherapy was initiated, with marked improvement in lactate.

Conclusions: In cancer cells, glucose metabolism switches from the oxidative pathway to the glycolytic pathway, causing the accumulation of lactic acid, a phenomenon called the Warburg effect (WE). Type B lactic acidosis is a rare presentation of hematological malignancies, especially in children. We encourage providers to investigate all patients with unexplained lactic acidosis for an ongoing oncologic emergency. Early diagnosis and administration of chemotherapy could mean the patient's survival.

Keywords

Lactic acidosis, Leukemia, Warburg effect, Pediatric

Abbreviations

meq/L: Milliequivalent/liter; U/L: Units/Liter; mg/dL: Milligram/Deciliter; mmol/L: Millimoles/Liter; g/dL: Gram/Deciliter; µL: Microliter; mmHg: Millimeters Mercury

Highlight Box

Key findings

- Pediatric Leukemia can rarely present with just severe Type B lactic acidosis.

What is known and what is new?

- Cancer can present with severe Type B lactic acidosis but is rarely seen as the presenting abnormality in a new diagnosis of Leukemia. This case report is a rare presentation of Type B lactic acidosis in newly diagnosed Pediatric Leukemia.

What is the implication, and what should change now?

- Evaluation for a malignancy should be initiated in cases of otherwise unexplainable lactic acidosis and relatively well appearing patient. Early diagnosis and treatment could count towards patient survival.

Case Report

Introduction

Lactic acidosis is defined as a pH of less than 7.35 and elevated blood lactate levels. Upper limits of normal lactate levels vary by laboratory from 0.5 to 2.2 mmol/L. Hyperlactatemia is most commonly attributable to tissue hypoxia as seen in conditions such as sepsis and referred to as Type A lactic acidosis. However, hyperlactatemia also rarely occurs secondary to other mechanisms, such as aerobic glycolysis, a term denoting stimulated glycolysis that depends on factors other than tissue hypoxia and is referred to as Type B lactic acidosis [1]. Type B lactic acidosis is rarely seen in patients with hematological malignancies, and it is attributed to increased tumor burden, rapid progression and poor prognosis [2].

The Warburg effect (WE), first described by Otto Walburg in the early 20th century, is a phenomenon by which cancer cells have the innate ability to

maintain a high glycolytic rate even in conditions of adequate oxygen supply. We report a case of Type B lactic acidosis in a 17-year-old male presenting with emesis and abdominal pain [3,4] who was diagnosed with T-cell Acute Lymphoblastic Leukemia (ALL). The initiation of chemotherapy led to the resolution of lactic acidosis. We present this report to assist clinicians with diagnosing cancer in the setting of Type B lactic acidosis. This manuscript is written following AME case series checklist (available at CARE-checklist-English.docx (live.com)).

Case Description

A previously healthy 17-year-old male presents with five days of body aches, headache, nausea, non-bilious, non-bloody vomiting, and poor oral intake to an outside Emergency Department. Initial diagnostic evaluation revealed a complete blood count with leukocytosis with a white count of 22,000 μ L, mild transaminitis (> 60 U/L), negative nitrites and leukocyte esterase in the urine, bicarbonate level of 9 mmol/L, and creatinine of 1.3 mg/dL and elevated lipase level of 893 U/L. Imaging of the CT abdomen and pelvis revealed heterogenous nephograms of both kidneys without hydronephrosis or hydroureter and findings concerning for pyelonephritis (Figure 1). The patient was transferred to a tertiary care hospital for admission.

On admission to the pediatric acute care unit, the patient continued to look tired and mildly tachycardic, with pertinent laboratory abnormality including bicarbonate < 10 mmol/L, normal complete blood count except leukocytosis and bands 8%, elevated lactate dehydrogenase > 500 U/L, procalcitonin 0.71 ng/ml and CRP 1.7 mg/dL. A repeat MRI of the abdomen showed diffuse bilateral abnormal renal parenchymal signal intensity and enhancement concerning for pyelonephritis.



Figure 1: CT Abdomen: Abnormal enhancement of the kidneys, left kidney worse than the right kidney. Favor pyelonephritis but infiltrative process is in the differential given atypical appearance.

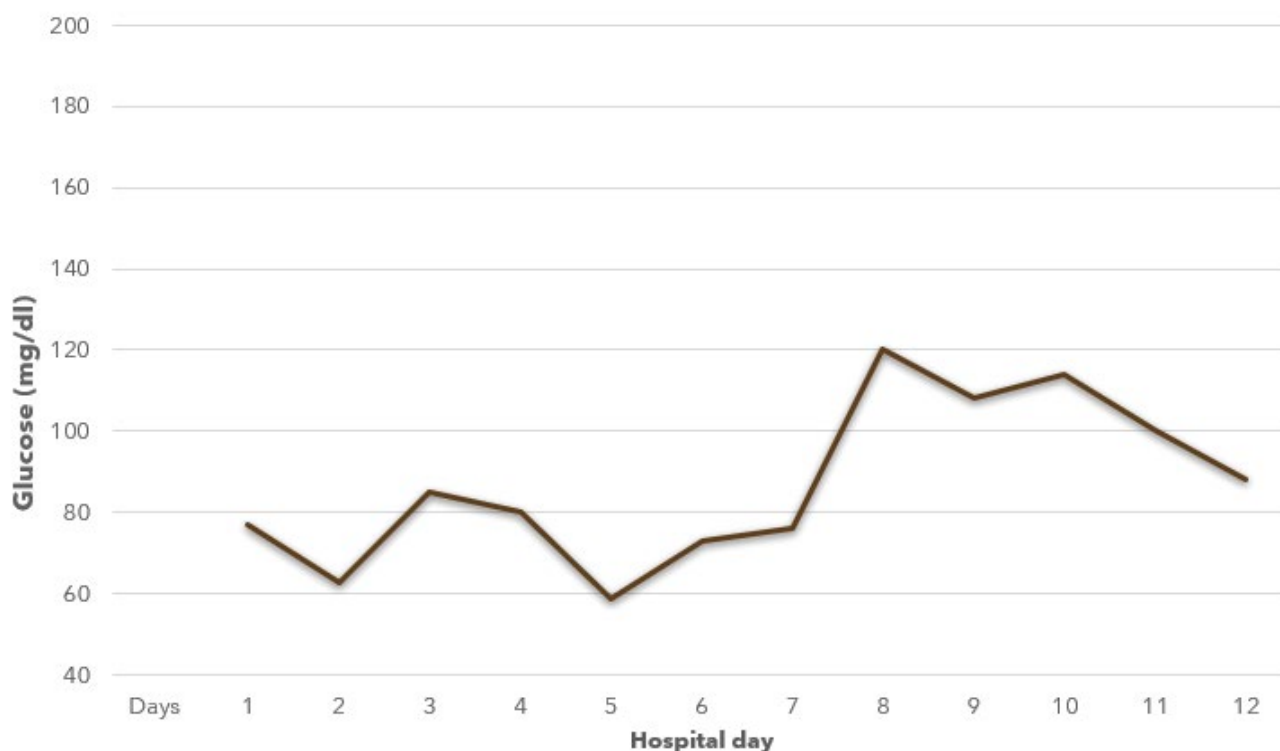


Figure 2: Trend of blood glucose level throughout the hospital stay.

The patient was continued on intravenous antibiotics pending blood and urine cultures. Aggressive fluid resuscitation was started. After initial fluid resuscitation, a complete metabolic panel was repeated, showing a persistent anion gap and a lactic acid level of 12.2 meq/L which was confirmed on blood gas. Due to the ongoing lactic acidosis despite fluid resuscitation, the patient was transferred to the intensive care unit (ICU) for evaluation and closer monitoring.

In the ICU, arterial blood gas was repeated with profound lactic acidosis of 13.5 meq/L and pH 7.13. The patient had unchanged vital signs. Physical examination revealed no signs of global or local hypoperfusion (normal blood pressure, normal capillary refill and absence of mottling). Additional physical examination was significant for small mobile posterior auricular and submandibular lymph nodes on the left side. The initial presentation and laboratory values were concerning for septic shock. Still, given negative blood culture, negative urine culture, and a procalcitonin level within normal limits at 0.71 ng/ml, the differential diagnosis now included other causes of hyperlactatemia secondary to Type B lactic acidosis. The drug screen was negative for most common ingestions causing anion gap metabolic acidosis, including salicylate, antibiotics, antiviral drugs, ethylene glycol, methanol, propylene glycol (a solvent used in many drugs including lorazepam, etomidate, nitroglycerine, and phenytoin).

Additionally, there was no associated history of accidental or intentional ingestion. Further evaluation recommended by the toxicology service was negative.

Nephrology was consulted, and they recommended continuing to give the patient sodium bicarbonate containing intravenous (IV) fluids given a high anion gap metabolic acidosis (HAGMA).

Dextrose was added to fluids because of lower blood glucose levels between 60-90 mg/dL throughout the stay (Figure 2), and due to an unclear cause of lactic acidosis, intravenous thiamine was also added to the management. At this point, the patient had life-threatening lactic acidosis of unknown etiology with no evidence of toxic ingestion or evidence of infection on the blood cultures. Suspicion was increased for a hematological malignancy causing lactic acidosis due to the Warburg effect. Therefore, the oncology service was consulted and recommended a CT chest, which showed a heterogeneous mass in the anterior mediastinum measuring 6.1 × 3.0 cm transaxial extending to the left neck base, displacing the trachea to the right (Figure 3), suspicious for cancer. Biopsy of the mediastinal mass subsequently revealed T-cell lymphoblastic lymphoma, and bone marrow aspirate of the right posterior iliac crest had 23% blasts. A positron emission tomography scan (PET) done on Day 6 of admission revealed metastatic disease throughout the head/neck, chest, abdomen, and pelvis (Figure 4), confirming the diagnosis of T-cell leukemia. Lumbar puncture performed on day 1 of therapy was positive for leukemia cells, 11% leukemia blasts cells. By Day 5 of Induction treatment, the anion gap had resolved with a lactic acid level < 5 milliequivalent per liter with no further recurrence during the hospital stay (Figure 5).



Figure 3: CT chest with contrast showing heterogeneous mass in the anterior mediastinum measures 6.1 × 3.0 cm trans-axial.

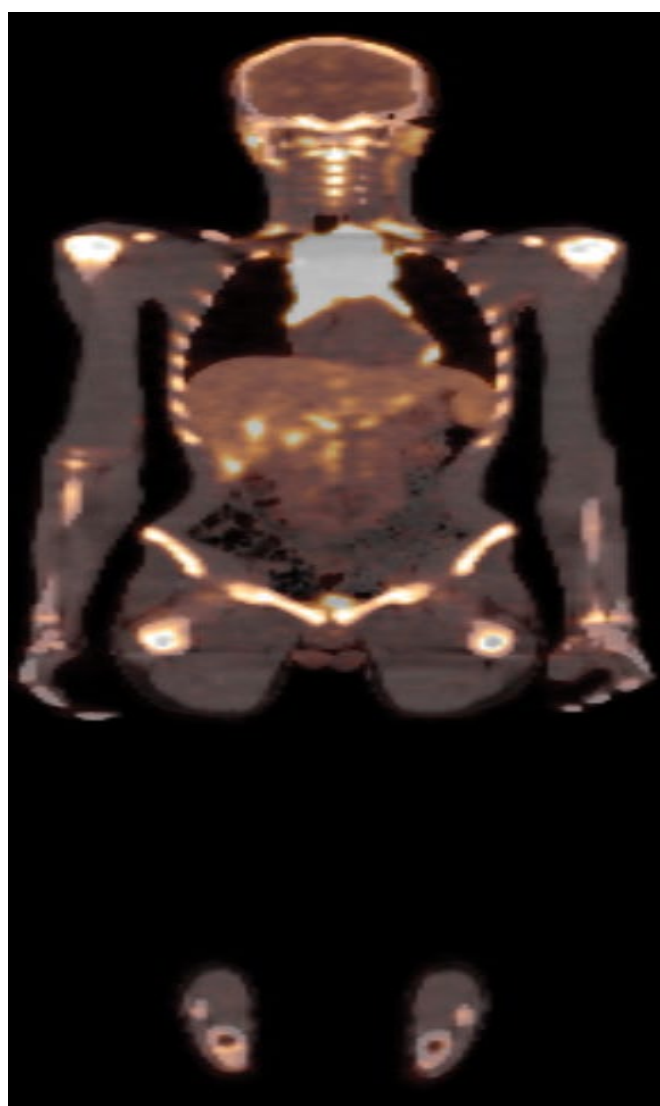


Figure 4: PET scan showing metastatic disease throughout the head/neck, chest, abdomen and pelvis. Extensive osseous metastatic disease.

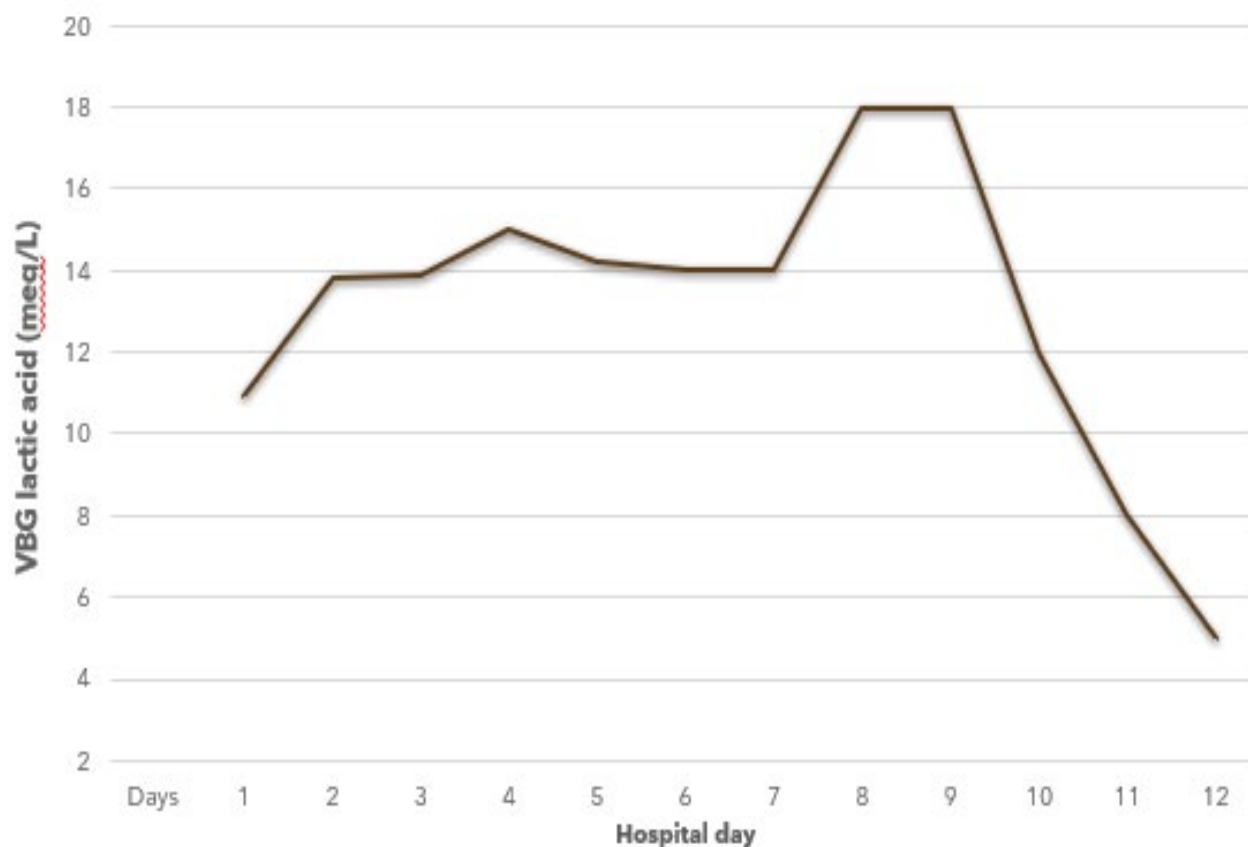


Figure 5: Trend of lactic acid level before and after the initiation of chemotherapy. Milliequivalent/liter (meq/L).

Discussion

Lactic acid is a by-product of glucose metabolism, usually seen in the absence of sufficient oxygen and normally formed in skeletal muscle, red blood cells, and brain and metabolized to form water and carbon dioxide in the liver and kidneys during anaerobic exercise conditions [5,6]. Normally, glucose is broken down through glycolysis in the cell cytoplasm, generating pyruvate, converted to lactic acid during anaerobic glycolysis with less ATP generated than oxidative phosphorylation. However, in an oxygen-rich environment, the pyruvate in the cytoplasm will enter the mitochondria and metabolize to generate 36 ATP molecules per glucose molecule through aerobic glycolysis [7,8]. In some cancer cells, this glucose metabolism switches from the oxidative pathway to the glycolytic pathway, causing the accumulation of lactic acid. This phenomenon was initially described by Otto Warburg in the 1920s and is called aerobic glycolysis or the Warburg effect (WE). Later, in 2000, more work was done on the association between lactate levels and ongoing malignant processes [4,9,10]. A study by Pavlides, et al. showed that if the tumor itself doesn't have the ability of aerobic glycolysis, it can induce the surrounding fibroblastic stroma to induce WE and thus provide necessary energy-rich nutrients to facilitate tumor growth and angiogenesis, a phenomenon called "Reverse Warburg Effect" [11,12].

There are several hypotheses as to why cancer cells switch to aerobic glycolysis. Cancer cells tend to consume glucose at a much higher rate than normal cells, leading to glucose exhaustion. Extracellular lactate and acidosis in the tumor microenvironment potentiate surrounding tissue invasion, angiogenesis, provide nucleotides, amino acids, lipids and hexosamines as building blocks for the new cells, produce the desired amount of energy for the cancer cells in a shorter time and by producing more NADPH via pentose phosphate pathway they maintain redox homeostasis [13,14]. Lactic acidosis also reprograms the cells' metabolism by avoiding glucose starvation, leading to prolonged cell survival and apoptosis inhibition, and providing substrate for intratumoral aerobic cell metabolism [15-17]. The altered functional metabolism of the cancer cells is also attributed to biochemical aspects of the Warburg effect, like activation of the Hypoxia inducible factor 1 alpha (HIF-1 α), which in turn upregulates the glycolysis and downregulates the oxidative phosphorylation [18-20]. Studies have also shown that the increased expression of glucose transporters on the cell surface of cancer cells adds to a higher rate of glycolysis from cancer cells. This phenomenon is also often used in diagnostic techniques like FDG-PET [21]. In 2014, Xie, et al. described the dual metabolic nature of cancer cells depending on the microenvironment conditions, i.e., they can switch between aerobic glycolysis and oxidative

phosphorylation to meet their metabolic demands [22]. Other important regulatory mechanisms established to sustain aerobic glycolysis include inactivation or loss of function of the tumor suppressor like p53, oncogenes activation and inactivation of the AMP-activated protein kinase signaling pathway [14]. All the above mechanisms make the environment of the cancer cells most viable for cell multiplication and effective, fast metabolism via aerobic glycolysis/WE.

Type B lactic acidosis is a rare primary presentation of hematological malignancies like ALL, especially in children [23-25]. Adult case reports of solid tumors describe LA as an oncological emergency [26-29]. Ruiz, et al. between 2000 and 2010, identified 31 cases of lactic acidosis secondary to malignancy and found 87% were hematological in origin, with lymphomas being the most prevalent. Of all the cases reported, more than 90% of the pediatric cases were lymphoma or leukemia, with very few having a favorable outcome [30]. Several other case review series done in adults have also identified systemic lactic acidosis as a rapidly fatal metabolic complication requiring prompt identification and management [2,3,31].

The patient, in this case, at the time of presentation, had a high degree of lactic acidosis suggestive of tumor burden, with no findings in the history, physical examination and complete blood count suggestive of cancer to begin with. Nonspecific findings like elevated lactate dehydrogenase, mild transaminitis and leukocytosis with bandemia and no blasts on complete blood count was more suggestive of Type a lactic acidosis due to hypoperfusion. After the diagnosis of leukemia his end of induction minimal residual disease (MRD) was positive at 0.46%, with his MRD at the end of consolidation therapy being 0%. Our patient is now in remission, continuing treatment for three years.

Treating the underlying malignancy quickly resolves the acidosis. Therefore, early initiation of chemotherapy is important. In some cases, sodium bicarbonate infusions have been used as a bridging modality to chemotherapy. However, this is counterproductive in many cases, as sodium bicarbonate has deleterious effects on the inotropy of the heart [32]. Thiamine, a cofactor for pyruvate dehydrogenase that is responsible for converting pyruvate to acetyl coenzyme A and further to Krebs cycle, has been shown to improve lactic acidosis, especially in patients who are Thiamine deficient [33]. Hemodialysis has also been used for Type B lactic acidosis; however, the role in WE cases is controversial [34]. Our patient received sodium bicarbonate and thiamine before the initiation of chemotherapy without significant benefit. Only the initiation of chemotherapy had a direct impact on resolving lactic acidosis.

Conclusions

We identified a rare case of Type B lactic acidosis

in a newly diagnosed patient with pediatric T-cell ALL who had no other reason for elevated lactate levels and was clinically well appearing. Treatment of the underlying malignancy ultimately resolved the lactic acidosis. Evaluation for a malignancy should be initiated in cases of otherwise unexplainable lactic acidosis. Early diagnosis and administration of chemotherapy, in this case, resolved the lactic acidosis.

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Contributions

No financial disclosures or conflict of interest.

Conflicts of interest

None.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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