



Lactic acidosis as the initial manifestation of acute lymphoblastic leukemia: A case report.

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Abstract

Introduction: Lactic acidosis is a rare manifestation of acute lymphoblastic leukemia (ALL) in children; its pathogenesis is multifactorial and poorly understood. This association carries a fatal prognosis. Timely diagnosis and initiation of proper treatment for hematological neoplasia are the most critical factors in resolving this metabolic complication.

Clinical case: The case of a 5-year-old patient who was admitted to the emergency service with a month of generalized pallor, hyporexia, and ecchymosis is presented. Twenty-four hours before, he had respiratory distress and acidotic respiration. The physical examination found cervical and inguinal adenopathies.

Diagnostic workshop: biometry was performed with white blood cells of $9.10 \times 10^9/\mu\text{l}$, neutrophils 41.6%, lymphocytes 44.6%, DHL 494 u/L, total bilirubin 0.33 mg/dl, potassium 2.55 mEq/L, sodium 134 mEq/L, calcium 11.8 mg/dl, TGP 16 U/L, Ac uric 4.7 mg/dl, urea 33 mg/dl, creatinine 0.99 mg/dl, pH 7.15, pCO₂ 18 mmHg, pO₂ 58.6 mmHg, HCO₃ 6.2 mmol/L, excess base -20.4 mmol/L, and lactate 10 mmol/L. Normal kidney ultrasound. Bone marrow biopsy revealed pre-B stage acute lymphoblastic leukemia.

Evolution: Type B metabolic acidosis was treated with intravenous hydration and bicarbonate. She was referred for specific hemato-oncological treatment.

Conclusions: In the present case of persistent metabolic acidosis without evidence of tissue hypoperfusion, the differential diagnosis of hematological malignancies was considered.

Keywords: MeSH

Cell Lymphoblastic Leukemia-Lymphoma Precursor; Acidosis; Neoplasms; Case Reports.

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Introduction

Metabolic acidosis is a decrease in serum bicarbonate concentration of less than 21 mEq/L and a pH of less than 7.35. Arterial blood gases and serum lactate levels are used to establish the diagnosis [1, 2].

In patients presenting with lactic acidosis without clinical evidence of tissue hypoperfusion or refractory to traditional treatment, the differential diagnosis with hematological malignancies should be considered [1, 3].

Lactic acid is a breakdown product of glucose under anaerobic conditions, where pyruvate is converted to lactate. There are two types: hypoxic (type A) and nonhypoxic (type B). The type associated with malignancy is often type B [4].

Aerobic glycolysis occurs in malignant cells, producing lactic acidosis (LA) in the presence of oxygen, known as the Warburg effect. Cancer cells can maintain a high rate of glycolysis even in the presence of oxygen and produce excess lactate [1].

Some studies suggest that many factors contribute to this high rate of glycolysis. One is the overexpression of glycolytic enzymes, such as hexokinase. Overexpression of a mitochondrial-bound type II hexokinase with increased affinity for glucose allows tumor cells to proliferate and survive for prolonged periods [2, 5].

Clinical case

Clinical history

A male 5-year-old infant patient with no significant personal or family history. He was admitted to the emergency department reporting a clinical picture of one month of evolution characterized by generalized paleness, hyporexia, and ecchymosis in the lower extremities of spontaneous appearance; 24 hours before, he presented respiratory distress, so his admission to our unit was decided.

On arrival at the emergency room, she presented generalized paleness, heart, and respiratory rates in the

90th percentile for age, with acidotic respiration. The physical examination revealed cervical and inguinal lymphadenopathy and ecchymosis.

Diagnostic workshop

The results of the laboratory tests upon admission are shown in Table 1, where metabolic acidosis with elevated anion Gap (AG), hyperlactatemia, severe hypokalemia, and acute renal failure are presented.

Initial treatment

As the first intervention, oxygen support was placed by nasal cannula, intravenous hydration plus bolus administration of potassium at 0.5 mEq/L, and replacement of bicarbonate in a bolus, later loading of the sixth molar and excess base calculus. The patient improved hemodynamically, and progressive weaning from oxygen support was begun, in addition to the recovery of renal function; however, metabolic acidosis persisted with elevated AG and increased lactate (Table 2) despite correction with bicarbonate, indicating management in a critical area due to the risk of clinical deterioration.

Assessed by the nephrology service where a renal Doppler ultrasound was requested (Figure 1); reported normal and ruling out renal compromise, which is why intravenous hydration with bicarbonate contribution is indicated without the need for dialysis management.

His imaging studies included chest and abdominal tomography; both were found to be normal. Possible causes of lactic acidosis, such as hypoperfusion, liver failure, poisoning, sepsis, and kidney disease, were ruled out, so the approach was expanded to screen for infiltrative syndrome (Table 3) with peripheral blood smears, in addition to consulting the pediatric hematology service, who indicated bone marrow aspirate (immunophenotype and translocation panel).

Table 1. Laboratory tests on admission.

Hematic biometry	Hemolysis Profile	Venous blood gases	Metabolic profile	Renal function	General urine test
White Blood Cells 9.10 x10 ⁹ /ul	Reticulocytes 2.77% (corrected 1.89%)	pH 7.15	Potassium 2.55 mEq/L	Urea 33 mg/dl	Clear appearance
Neutrophils 41.6%	Lactic dehydrogenase 494 U/L	PCO ₂ 18 mm/Hg	Sodium 134 mEq/L	Creatinine 0.99 mg/dl	DU 1005
Lymphocytes 44.6%	Total bilirubin 0.33 mg/dl	PO ₂ 58.6 mm/Hg	Calcium 11.8 mg/dl	GFR 62 ml/min/1.73	pH 5
Monocytes 11.9%	Direct bilirubin 0.16 mg/dl Indirect bilirubin 0.17 mg/dl	HCO ₃ 6.2 mmol/l	TGO 30 U/L TGP 16 U/L	FeNA 4%	Negative esterases and nitrites
Eosinophils 0.7%		BE -20.4 mmol/l	Uric acid 4.7 mg/dl	IFR 6.6%	Negative leukocytes
Hemoglobin 8gr/dl		lactic acid 15	Ammonium 35.80 ug/dl	Creatinine U/P 8.3	
Hematocrit 24%		Anion Gap 27.8	Proteins 5.91 g/dL	Urinary sodium 56 mEq/l	
VCM 78.3 fl					
HBCM 27.6 pg					
Platelets 174x10 ⁹ /ul					

Table 2. Serial control blood gases.

	02/19/23	02/20	02/21	02/22	02/24/23	02/25/23	02/26	02/27	02/28	03/01	03/02/23
pH	7.30	7.33	7.33	7.34	7.16	7.20	7.20	7.34	7.09	7.31	7.15
pCO ₂	24.1	23.9	28.9	33.1	28.4	14.8	17.6	27.2	15.3	20.7	15.3
pO ₂	34.9	74.9	66.9	70.3	71.7	110.5	77.8	54.6	67.4	179.4	90.8
HCO ₃ ⁻	11.8	12.4	16	17.6	10	5.7	6.7	14.5	4.6	10.3	5.3
BE	-12.4	-11.3	-7.9	-6.9	-17.1	-19.5	-18.8	-9.4	-22.9	-13.5	-21.5
AG		24.6	23	22.4	25	25.3	25.3	22.5	28.4	22.7	27.7
Lactic acid		10.3	9.5	9.5	13.5	17.7	13.9	9.6	17	10.3	

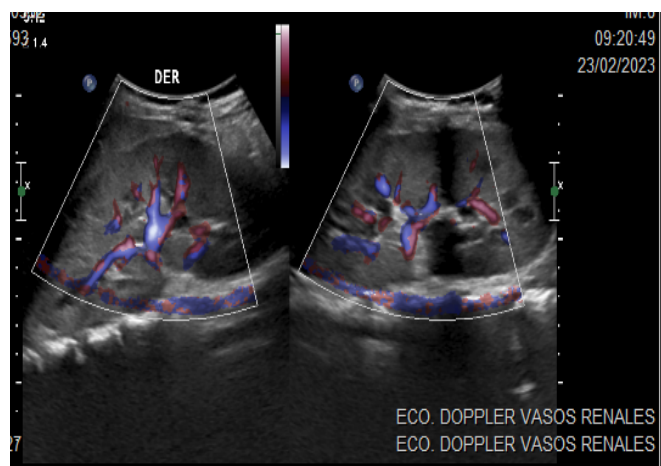
Table 3. Screening for infiltrative syndrome.

Peripheral blood smear: Red series Anisocytosis ++ Target cells ++, White series with atypical lymphocytes 8% without cytopenias

Myelogram: Hypocellular +/Dilute+ with presence of lymphoblasts type L2 (10%) – L3 (90%), 200 cells are counted

Myelogram with 90% of the L3 lymphoblasts of the FAB (French-American-British) classification, leading to the diagnosis of L3 acute lymphoblastic leukemia (image II) with subsequent immunophenotype results that detail the following: In a bone marrow sample received, 36.16% of immature cells (CD45+deb, nTdT++) were detected expressing characteristic B line markers (CD19++, CD79a++, CD22++), in the absence of myeloid and T line markers.

These cells express CD10+++ in a very intense and homogeneous way. The light scattering characteristics show cells compatible with cells of small size and low complexity. A bone marrow sample is concluded with two clones of B lymphoblasts in a consistent Pre B stage acute lymphoblastic leukemia phenotype (Figure 2).

Figure 1. Doppler ultrasound of renal vessels.

Evolution

The metabolic acidosis improved progressively with hyperhydration, a constant intravenous supply of bicarbonate, and initiation of the steroid window with dexamethasone 9 mg/m²/day every 6 hours. Once the patient was stabilized, he was transferred to the oncological hospital (SOLCA-Guayaquil) to continue managing the underlying disease.

Discussion

Common metabolic complications of acute lymphoblastic leukemia are hyperuricemia, hyperphosphatemia, hyperkalemia, hypo/hypercalcemia, and renal failure. Lactic acidosis is rare and unusual but can also present as an initial manifestation. It is diagnosed with serum lactate levels >5 mmol/L and pH <7.30. It is due to the imbalance in lactic acid production and its elimination by the liver and kidneys. [1, 2, 3, 6, 7]

In 1975, Cohen and Woods classified LA into Types A and B: Type A is due to hypoxia and impaired perfusion; the causes are sepsis, heart failure, and shock with multiple organ failure. Type B is caused by renal and hepatic failure, diabetes mellitus, neoplasms, thiamine deficiency, drugs and toxins that affect the

electron transport chain, and congenital metabolism abnormalities [8, 9].

The Warburg effect (WE) is a classic but challenging cause of LA type B in hematologic malignancies. This is due to a specific metabolism of malignant cells, where lactic fermentation predominates over oxidative phosphorylation, regardless of the oxygen level. It has mainly been associated with lymphoma, acute leukemia, chronic lymphocytic leukemia, chronic myelomonocytic leukemia, or multiple myeloma [5, 8].

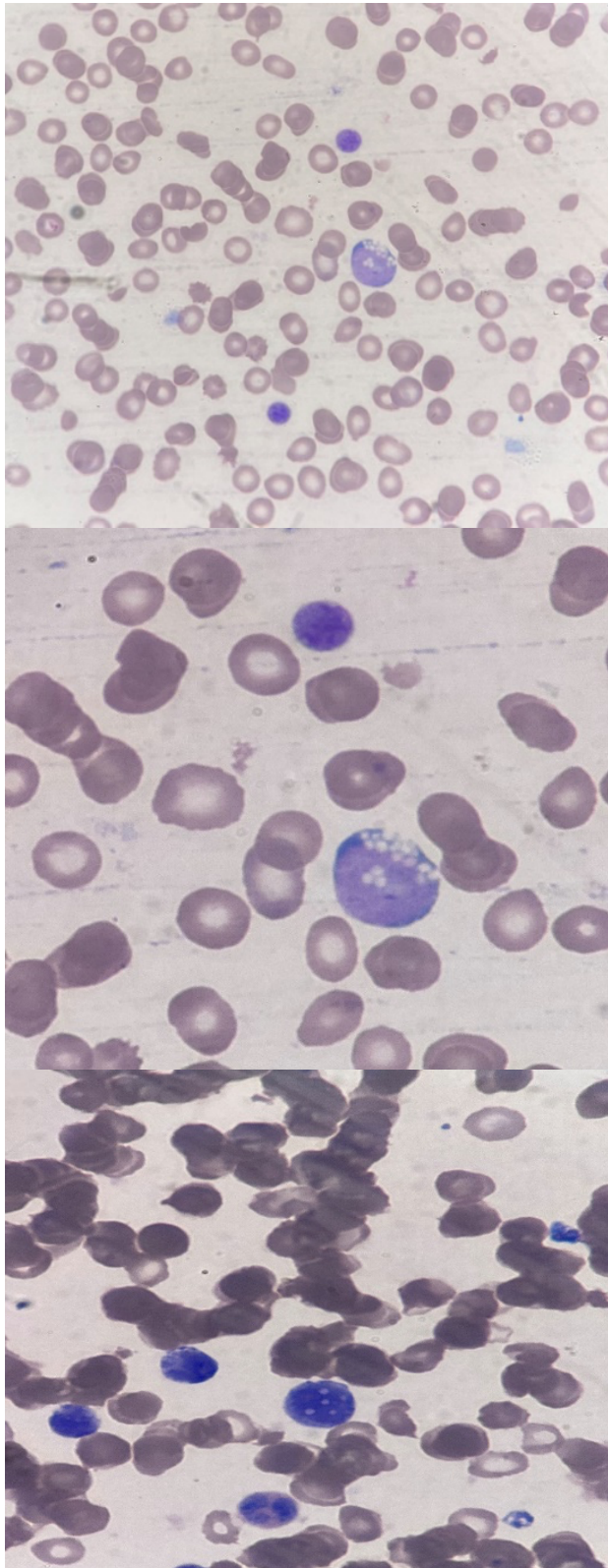
There are four suggested theories for the Warburg effect: cell signaling, adenosine triphosphate synthesis, biosynthesis, and the tumor microenvironment. The Warburg effect occurs in leukemia with the help of enzymes such as pyruvate kinase M2 (PKM2), lactate dehydrogenase A (LDHA), pyruvate dehydrogenase kinase 1 (PDK1), and fibroblast growth factor receptor 1 (FGFR1) [5, 8].

Cancer cells can produce excess lactate due to their high rate of glycolysis. The IGF-IGFBP system is thought to be involved in signaling that induces overexpression of a glycolytic enzyme, hexokinase [2, 5].

Insulin typically regulates the expression of this enzyme. However, IGFs and their receptors, which are overexpressed by some cancer cells, can mimic many activities of insulin. Insulin-like growth factors and their receptors are essential in controlling cancer cell proliferation and metabolism. Insulin-like growth factor I (IGF-I) induces hexokinase expression in a concentration- and time-dependent manner [5].

In a study by Sillos et al., patients had abnormally low plasma concentrations of IGF-I, IGF-II, and IGFBP-3 and elevated concentrations of IGFBP-1 and IGFBP-2; these abnormalities were proportional to the degree of disease activity. The same findings, except increased IGFBP-1, correlate with disease activity in other patients with leukemia and lymphoma [5].

Figure 2. Myelogram is compatible with L3 lymphoblasts of the FAB (Franco-American-British) classification.



Recently, oncogenes such as FLT3 tyrosine kinase, K-ras, c-Myc, and Bcr-Abl have been shown to induce glycolysis or mitochondrial dysfunction that promotes the Warburg effect. Among the clinical manifestations of LA, we found hyperventilation and hypotension associated with tachycardia, muscle weakness, vomiting, diarrhea, and stupor, symptoms compatible with our clinical case [2, 3, 6].

Conventional treatment of type B LA usually focuses on stopping or reversing the offending agents or improving the underlying organ dysfunction. The main treatment strategies for metabolic acidosis in a leukemic patient include intravenous fluids, alkalinization with bicarbonate infusion, chemotherapy, dialysis, and intravenous thiamine. Dialysis is recommended in severe cases of metabolic acidosis, such as the rest of the patients [1, 8, 9, 10].

Chemotherapy is the mainstay of treatment because this type of LA is usually refractory to conventional therapy, requiring close monitoring to avoid complications. A study by Ruíz et al. reviewed 31 case reports of LA type B secondary to neoplasms between 2000 and 2010. Most cases were hematological neoplasms (87%), and only 19% were children. Although 18 patients received chemotherapy, only five had a favorable outcome [3, 10].

Other authors, such as Sillos et al., Lozano Rodas et al., and Hayek M et al., support that chemotherapy with debulking of the primary malignancy resolves LA in some patients [2, 7, 8, 10].

Conclusions

Lactic acidosis as a complication or debut of LA can be considered a medical enigma. Its incidence is unknown, although it is known to be more frequent in adults than in children, but in both cases, it is associated with a poor prognosis.

When faced with a patient with persistent metabolic acidosis without clinical evidence of tissue hypoperfusion and refractory to traditional treatment, it is necessary to consider hematological malignancies as

part of the differential diagnosis. In this way, an initial suspicion becomes imperative for timely detection and proper management of these patients, thus avoiding delays in diagnosis.

Abbreviations

LA: lactic acidosis.

Supplementary information

No supplementary materials are declared.

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Does not apply.

Author contributions

Karla Calderón-Salavarría: Conceptualization, Data conservation, Acquisition of funds, Research, Resources, Software, Writing - original draft.
Robinson Ramirez-Ruiz: Conceptualization, Data conservation, Supervision, Fund acquisition, Research, Resources.
Liliam Campoverde-Coronel: Conceptualization, Supervision, Funding acquisition, Research, Resources.

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All the authors have read and approved the final version of the manuscript.

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Availability of data and materials

The data sets generated and analyzed during the current study are not publicly available due to clinical case confidentiality.

Statements

Ethics committee approval and consent to participate

Not required for clinical cases.

Publication Consent

The authors have permission for publication from the patient's parents.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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