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Acute Lymphoblastic Leukemia Presenting with Liver Infiltration and Severe Lactic Acidosis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 58
Final Diagnosis: Acute lymphoblastic leukemia
Symptoms: Chest pain • fatigue • loss of appetite • shortness of breath
Medication: —
Clinical Procedure: Liver biopsy and bone marrow biopsy
Specialty: Hematology

Objective: Rare disease

Background: Type-B lactic acidosis is a rare complication of solid tumors and hematological malignancies. It occurs secondary to Warburg effect, when glucose metabolism in cancer cells switches from the oxidative pathway to the glycolytic pathway. Malignant lactic acidosis is a life-threatening condition if not promptly diagnosed and treated urgently.

Case Report: We report the case of a 58-year-old male patient who presented with severe chest pain, dyspnea, systemic symptoms, leukopenia, normocytic anemia, and severe lactic acidosis. He was admitted with a possible diagnosis of acute pericarditis and lactic acidosis. Sodium bicarbonate replacement did not improve the lactic acidosis. Liver biopsy was performed because of persistently elevated alkaline phosphatase and gamma-glutamyl transferase; the biopsy showed atypical lymphoblasts and bone marrow biopsy confirmed the diagnosis of precursor B acute lymphoblastic leukemia. Lactic acidosis normalized after initiation of chemotherapy.

Conclusions: Cancer, particularly hematological malignancy, should be considered as an etiology and differential diagnosis of type-B lactic acidosis. Prompt recognition and urgent initiation of specific therapy to control the underlying malignancy are critical to manage this serious metabolic complication.

MeSH Keywords: Acidosis, Lactic • Hepatic Infiltration • Precursor B Cell Lymphoblastic Leukemia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/907383

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Background

Lactic acid is the metabolic product of anaerobic glycolytic metabolism and is excreted by the liver and kidneys. Lactic acidosis (LA) is defined as a pH of less than 7.35 and a plasma lactate level of more than 5 mmol/L [1]. It is considered a medical emergency. There are 2 types of LA: Type-A LA is associated with a state of poor tissue oxygenation (shock, tissue ischemia, etc), but Type-B LA is not associated with poor tissue oxygenation and occurs in conditions like liver disease, drug effects, toxins, thiamine deficiency, and malignancy (Table 1) [2]. It occurs secondary to Warburg effect, when glucose metabolism in cancer cells switches from the oxidative pathway to the glycolytic pathway. The mechanism of this effect is not fully understood, but it may be partly explained by enhanced glycolytic activity in the cancer cells triggered by the expression of hypoxia-inducible factor-1 alpha. This changes the metabolism of glucose from oxidative to glycolytic pathway and can produce lactate at a high rate [3,4].

LA associated with hematological malignancies is a rare condition and we found less than 100 reported cases of LA in the literature. Here, we present a case of severe LA, with cytopenias and liver dysfunction, which proved to be acute lymphoblastic leukemia (ALL).

Table 1. Causes of lactic acidosis.

Type-A: Hypoperfusion
Massive hemorrhage
Hypovolemia
Septic shock
Type-B: Overproduction or decreased clearance
Malignancy
Thiamine deficiency
Alcohol
Drugs: Metformin, antiretroviral, salicylates, INH
Liver or kidney failure
Diabetes mellitus
Toxin: cyanide
Hereditary: pyruvate carboxylate deficiency, pyruvate dehydrogenase deficiency, oxidative phosphorylation deficiencies

Case Report

A previously healthy 58-year-old man was admitted with severe chest pain for 3 days associated with shortness of breath. He complained of fatigue and loss of appetite for 3 months and he had lost 25 kg body weight during the last 2 months. On examination, he was hemodynamically stable and afebrile. There was mild epigastric tenderness. There was no lymphadenopathy or hepatosplenomegaly.

The complete blood count showed a white blood cell 3.8×10^9/L (normal 4–11), hemoglobin 7.3 g/dl, MCV 99, MCH 33, and platelet count 219×10^9/L. The differential white cell count showed neutrophils 3.0×10^9/L, lymphocytes 0.8×10^9/L, and peripheral blood film showed no immature cells. The coagulation profile was normal. Blood chemistry showed a blood urea nitrogen 5.6 mmol/L, serum creatinine 146 µmol/L, and albumin 24 g/L. Liver function tests showed aspartate aminotransferase 55 IU/L, alanine aminotransferase 18 IU/L, total bilirubin 4.9 µmol/L (normal up to 18 µmol/L), alkaline phosphatase (ALP) 215 U/L (normal 50–136), gamma-glutamyl transferase (GGT) 315 U/L (normal 5–55), and a raised lactate dehydrogenase at 787 U/L (normal 81–234).

Blood gases showed pH 7.28, $PvCO_2$ 31 mmHg, PvO_2 35 mmHg, bicarbonate 14 mmol/L, and base excess of –10.9. Serum sodium was 133 mmol/L, potassium 4.3 mmol/L, chloride 97 mmol/L, the anion gap was 19.3 mEq/L, and lactic acid was 13.5 mmol/L (normal less than 2.0). The random plasma glucose level was 179 mg/dL. Insulin-like growth factor-1 (IGF-1) was 54 ng/ml (normal range 55–186) and thiamine level was 78 nmol/L (normal range 70–200). Cardiac enzymes showed a high BNP of 1104 pg/ml (normal <100), total creatine kinase 46 U/L (normal <171), and troponin <0.1 µgm/L.

There were no active infiltrative lesions on the chest x-ray. ECG showed ST segment changes suggestive of pericarditis. There was a thin rim of pericardial effusion on echocardiography.

CT scan of the chest and abdomen showed pericardial thickening with enhancement, consistent with pericarditis. There were multifocal hypodense lesions in both kidneys, suggestive of inflammatory process or metastatic disease. The liver was mildly enlarged, with homogeneous enhancement. There was no thoracic or abdominal lymphadenopathy.

The patient was referred to the ICU and started on sodium bicarbonate, but severe acidosis persisted in spite of bicarbonate replacement. A liver biopsy was performed on day 10 of hospitalization due to persistently elevated GGT and ALP, and abnormal findings on abdominal CT.

The liver biopsy showed atypical lymphocytic infiltrates in the portal tracts. These atypical cells were positive for B-lymphoblast markers CD79a, CD43, TdT, CD10, and CD4. They were negative for T cell and myeloid markers. All these

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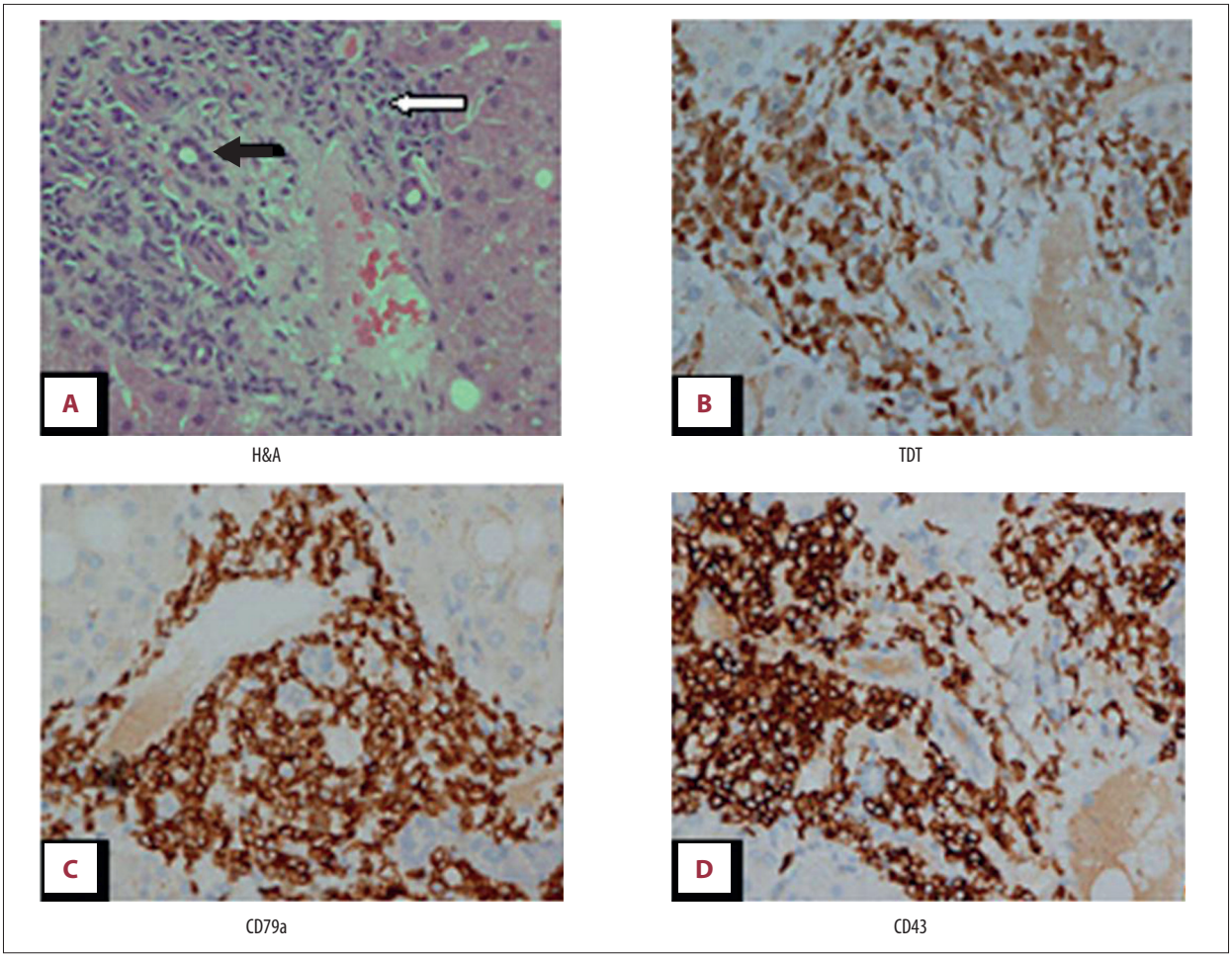

Figure 1. Liver biopsy: (**A**) H&E reveals infiltration of the portal tract (black arrow) by mainly small, rounded blast cells with scanty cytoplasm, round convoluted nuclei, fine chromatin, and inconspicuous nucleoli (white arrow). Immunohistochemistry revealed the infiltrative cells were positive for TDT, CD79a, and CD43 (**B–D**, respectively; ×400).

findings were highly suggestive of B-lymphoblastic leukemia/lymphoma (Figure 1).

A bone marrow examination was carried out and showed diffuse infiltration of the marrow by lymphoblasts, which constituted about 80% of all nucleated cells (Figure 2). These cells were positive for CD19, CD10, CD79A, HLA-DR, TdT, and cytoplasmic CD22, and they were negative for other lymphoid and myeloid markers. These findings confirmed the diagnosis of precursor B acute lymphoblastic leukemia (ALL).

The patient received bicarbonate replacement, IV hydration, broad-spectrum antibiotics, and analgesics. Initially, there was no improvement in his condition, but the creatinine level dropped to 88 µmol/L after 3 days of hydration.

After confirmation of ALL diagnosis, he was started on induction chemotherapy. On that day, the lactic acid level reached more than 15 mmol/L. After initiating the treatment, lactic acid

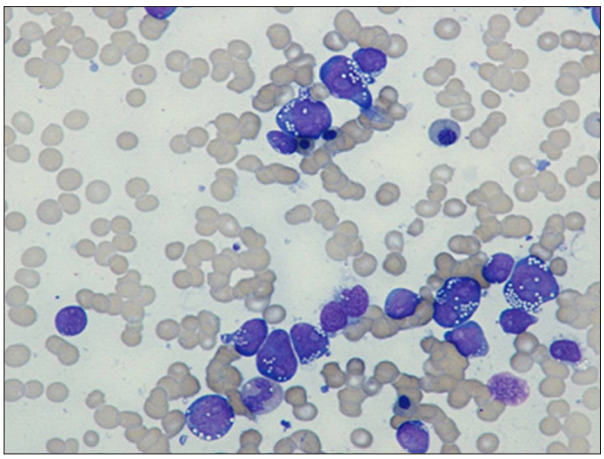

Figure 2. Bone marrow smear showing several lymphoblasts with a high nuclear to cytoplasmic ratio and variably condensed nuclear chromatin. Many of the lymphoblasts contain few to multiple cytoplasmic vacuolations (May-Grunwald-Giemsa ×60).

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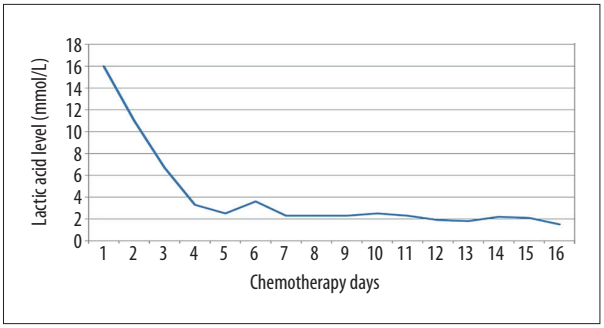

Figure 3. Relationship of lactic acid with therapy showing dropping of lactic acid level after starting the chemotherapy.

level started to decrease and dropped to 6.7 on day 3 of chemotherapy. It normalized on day 12 of chemotherapy (Figure 3). A bone marrow biopsy performed on day 14 showed hypocellular bone marrow with cellularity of 20–30%, and 30% lymphoblasts of the total marrow cells, consistent with inadequate response and residual disease. The initially planned treatment was continued, and a bone marrow biopsy was repeated on day 35 and showed markedly hypocellular bone marrow with <1% of blast cells by morphology, consistent with bone marrow remission. Flow cytometry did not detect any residual blasts.

The patient completed induction phase I and II, as well as intensification and consolidation phases. His treatment phases were complicated by 2 episodes of febrile neutropenia, PICC line-induced right brachial vein thrombosis, steroid induced hyperglycemia, proximal myopathy, and depression. As he was considered high risk because of his age, inadequate response, and residual disease on day –14, he was referred for allogeneic stem cell transplantation, but, unfortunately, no matched donor was found. Currently, he is in remission, going through the maintenance phase of therapy, and remains well.

Discussion

Lactic acid is a byproduct of glucose metabolism in a low-oxygen environment. Glycolysis ends by formation of pyruvate, which is converted to acetyl coenzyme-A to generate energy in aerobic conditions in the Krebs cycle. However, in anaerobic conditions, pyruvate is converted to lactate. Lactate is metabolized to form water and carbon dioxide in the liver and kidneys. LA results from an imbalance of production and metabolism of lactic acid [5]. Cancer cells can generate lactate at a high rate due to increased rate of glycolysis [6]. Many factors may contribute to the high rate of glycolysis, particularly aberrant expression or overexpression of glycolytic enzymes, such as hexokinase [7].

Neoplastic infiltration of the liver has been observed in the majority of reported cases of leukemia and lymphoma with LA [1]. The high frequency of liver involvement in these patients suggests that hepatic underutilization of lactate due to cancer infiltration is likely to be an important factor in the pathogenesis of most cases of cancer-associated LA.

The lactic acidosis in our patient was not explained by a hypoperfusion state, toxins, drugs, or thiamine deficiency. By exclusion, the cause of lactic acidosis in our case was most likely type-B LA secondary to "Warburg" effect in malignant cells. This happens when glucose metabolism in cancer cells switches from the oxidative pathway to the glycolytic pathway, causing accumulation of lactic acid. Furthermore, infiltration of the liver by lymphoblasts, confirmed by liver biopsy, and possible bilateral renal infiltration as suggested by CT scan, may have impaired the excretion of formed lactic acid, as the liver and kidneys are the primary sites of lactic acid excretion.

LA is a rare but life-threatening complication of hematological malignancies [8,9]. It is more commonly associated with aggressive lymphoid malignancies, but has been reported in multiple myeloma and other disorders [10]. The mortality rate of reported cases of LA associated with hematological malignancies has been very high; 25 of 27 patients with lymphoma and 24 out of 25 patients with leukemia eventually died [1]. The occurrence of LA remains a strong marker of poor prognosis. All patients whose disease was not treated or was not responsive to chemotherapy died with active LA. LA resolved only when chemotherapy caused cytoreduction of the underlying tumor. Therefore, the clearance of LA depends on the responsiveness of the underlying malignancy [1]. The dramatic decrease in the lactic acid level in our patient following initiation of chemotherapy strongly supports the above-mentioned hypothesis of type-B LA, as it corresponded to the clearance of leukemia blast cells by the chemotherapy (Figure 3).

This is an unusual case of ALL which presented with pericarditis-like features, liver infiltration, and severe lactic acidosis, and no blast cells in the peripheral blood. Furthermore, the most notable aspect of this case is the excellent response and complete resolution of lactic acidosis following initiation of chemotherapy. This is not the usual outcome of type-B LA, and most of the reported cases have been associated with high morbidity and mortality [1,6,9]. Whether our patient will continue in remission or eventually relapse remains to be seen.

Conclusions

Cancer, particularly hematological malignancy, should be considered in the differential diagnosis and etiology of type-B LA. Prompt recognition of this condition and early initiation of specific therapy (chemotherapy) are mandatory for a favorable outcome.

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Conflict of interest

None.

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