A rare metabolic complication of acute lymphoblastic leukemia in childhood: lactic acidosis

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A 13-year-old boy presented with nausea, fatigue, weight loss, and bone pain for two months. Complete blood count and serum renal and liver function tests were all normal. Blood gas analysis revealed severe metabolic acidosis with high anion gap. Lactate level was 61.2 mmol/L. Abdominal ultrasonography yielded bilateral nephromegaly and hepatomegaly with increased echogenicity. Peripheral blood smear revealed 2% blasts. Bone marrow aspiration showed 'Common ALL Antigen'-negative acute lymphoblastic leukemia by flow cytometric analysis. Metabolic acidosis dissolved as soon as chemotherapy was begun. Lactic acidosis at the presentation of acute lymphoblastic leukemia –especially with low tumor burden- is a very rare and almost always fatal complication. Our patient is still alive and in remission, which is a point of interest in this child.

Key words: lactic acidosis, acute lymphoblastic leukemia, metabolic, complication.

Lactic acidosis (LA) in childhood is mostly caused by tissue hypoperfusion or acute severe hypoxemia due to sepsis, dehydration and shock. It may also be seen as a result of renal failure, inborn errors of metabolism and intoxication[1].

Lactic acidosis (LA) at the presentation of acute lymphoblastic leukemia (ALL), especially with low tumor burden, is a rare complication and points to an unfavorable prognosis[2]. It is thought to develop by several mechanisms, including overproduction of lactate by blasts and/or decreased hepatic and renal clearance due to organ dysfunction. In a previous study, 25 leukemic patients presenting with LA were reported. Only seven of them were children and all died within several days after the initial diagnosis[3].

Herein, we report a 13-year-old boy presenting with LA who was diagnosed as ALL in order to highlight a rare metabolic complication of hematological malignancies.

Case Report

A 13-year-old boy presented with fatigue, nausea, weight loss, and bone pain for two months. He had been treated for anemia with enteral iron and vitamin B12 for two months. When intractable abdominal pain developed, he was admitted to our hospital. No history of drug or infection was present. Family history was also unremarkable for hereditary disorders.

He was pale and uncomfortable at first evaluation. No petechia, purpura or ecchymoses was detected. Mild tenderness with palpation was present on the abdomen. The liver was palpated 3 cm below the right costal margin. No splenomegaly was present.

Complete blood count revealed hemoglobin: 13.6 g/dl, white blood cells: 8.4 x 10^9/L and platelets: 256 x 10^9/L. Fasting blood glucose level was 97 mg/dl. Renal and liver function tests were also normal. Serum sodium and potassium levels were 139 mEq/L and 4.1 mEq/L, respectively. Serum lactate dehydrogenase (LDH) was 1115 IU/L. Blood gas analysis yielded severe metabolic acidosis with high anion gap (pH: 7.05, HCO_3: 9.3 mmol/L and base excess: -19). Lactate level was 62

mmol/L (range: 0-2.2 mmol/L). Urine pH was 5.5. Sedimentation rate and C-reactive protein were 4 mm/hour and 0.9 mg/dl, respectively. Urine and blood amino acid analysis revealed no abnormality. No improvement in metabolic acidosis was observed despite the bicarbonate replacement therapy on the second day.

Abdominal ultrasonography revealed bilateral nephromegaly and hepatomegaly with increased echogenicity, and the patient was consulted to the Pediatric Hematology Division in order to exclude renal involvement of lymphoma or leukemia. Peripheral blood smear yielded 2% atypical lymphocytes. The bone marrow aspiration exhibited 100% blasts with L1 morphology according to French-American-British (FAB) classification, and immunophenotyping revealed a diagnosis of CALLA-negative B-cell ALL. Cytogenetic analysis showed a normal karyotype. Cytological evaluation of cerebrospinal fluid showed no blasts.

Metabolic acidosis began to improve progressively when methylprednisolone (20 mg/kg/day) was started according to the modified St. Jude Total 15 chemotherapy protocol[4,5]. Minimal residual disease was $1x10^{-4}$ on the 15th day by three-color method. Nephromegaly and hepatomegaly had resolved at the following ultrasonography evaluation on the 14th day.

The patient is in his 64th week of continuation therapy with remission. LA did not re-develop during therapy.

Discussion

Hyperuricemia, hyperphosphatemia, hyperkalemia, and hypo/hypercalcemia are metabolic complications usually seen at the presentation of ALL with high tumor burden. However, LA is a rare metabolic complication seen in pediatric ALL especially with low tumor burden. Some possible theories have been proposed, including overproduction of lactate by cancer cells, decreased hepatic and renal elimination due to organ dysfunction and tissue hypoxia caused by microemboli due to cancer cells[3].

The insulin-like growth factor (IGF) signaling pathway has been recognized as playing an important role in the proliferation of cancer cells, which mostly prefer the anaerobic glycolytic pathway even in the presence of oxygen. Furthermore, hexokinase – the rate-limiting enzyme of the anaerobic glycolytic pathway - can also be promoted by IGFs, leading to aberrant production of lactate[6]. Sillos et al.[3] reported elevated plasma IGF binding protein (BP)-2 and IGFBP-3 levels in leukemic children presented with LA, pointing to the importance of the IGF signaling pathway.

Elevated serum tumor necrosis factor – alpha (TNF-alpha) concentrations have been reported in newly diagnosed children with acute leukemia[7]. TNF-alpha is also thought to play an important role in the overproduction of lactate. It may decrease the action of pyruvate dehydrogenase and inhibit the cytochrome-dependent electron transport system, leading to LA[8].

Approximately 90% of lactate is eliminated by hepatic metabolism and the remainder by the kidneys. Leukemic infiltration causes reduced perfusion, decreased filtration and delayed excretion, leading to organ dysfunction. Therefore, diminished elimination of lactate is another cause of LA[9].

A few pediatric ALL patients presenting with LA have been reported in the literature[3]. In our previous study, renal involvement at presentation was reported in 11.2% of leukemic patients; however, none had associated LA[10]. LA at presentation of hematologic malignancies usually points to poor prognosis. It is generally resistant to standard bicarbonate replacement therapy. However, in order to prevent cardiac effects, alkalinization should be continued. After cytoreductive therapy is initiated, LA usually begins to resolve gradually. Therefore, the prognosis is also dependent on the response. It has been noticed that all pediatric cases reported with LA were resistant to therapy and died[3,11,12]. We demonstrated the apparent cytoreductive effect of mega-dose methylprednisolone on leukemic blasts previously[5]. Fortunately, our case initially responded to steroid well and achieved remission with the remaining therapy. He is now in the 64th week of the maintenance part of the protocol.

The exact pathophysiology of LA at presentation or relapse of hematologic malignancies is still unclear. Some cellular signaling pathways

might play roles in its development, and further investigations are needed. In this brief communication, we want to emphasize an unusual presentation of ALL. Pediatricians should keep in mind hematological malignancies in the case of unexplained LA and evaluate the peripheral blood smear earlier.

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