

# ACUTE LYMPHOBLASTIC LEUKEMIA WITHOUT CIRCULATING BLASTS PRESENTING AS SEVERE HYPERCALCEMIA

Z. Oloomi\*

Department of Pediatric Oncology, Imam Khomeini Hospital, School of Medicine, Medical Sciences/University of Tehran, Tehran, Iran

**Abstract-** Hypercalcemia complicating malignancy is a rare complication in pediatric age group. In this article, we present a case with acute lymphoblastic leukemia presenting as severe hypercalcemia. A 10 years old girl presented with an acute onset of fever, nausea, vomiting, loss of weight, costovertebral pain and frequency. She was admitted with a presumptive diagnosis of acute pyelonephritis. Her examination showed mild hepatosplenomegaly. In laboratory studies she had severe hypercalcemia. Despite the absence of circulating blasts, bone marrow aspiration was diagnostic of acute lymphoblastic leukemia. The hypercalcemia was initially treated with intravenous hydration and furosemide but the serum calcium level normalized only after the beginning of specific chemotherapy. Hypercalcemia represents an emergency in children, and acute leukemia must be considered in differential diagnosis even when there are no circulating blasts.

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**Key words:** Acute lymphoblastic leukemia, hypercalcemia, childhood, chemotherapy

## INTRODUCTION

Hypercalcemia complicating malignancy is a frequent complication in adult patients, with an incidence up to 20% (1). Among hematopoietic malignancies, multiple myeloma and T-cell leukemia/lymphoma have a high incidence of hypercalcemia. The hypercalcemia associated with acute lymphoblastic leukemia (ALL) can be classified into two categories: those with or without bone metastases. The hypercalcemia in the absence of bone metastasis is associated with the action of factors such as interleukins and tumor necrosis factor (2) while hypercalcemia with bone metastasis is due to osteolysis subsequent to bone involvement.

Only a few cases of ALL with this metabolic abnormality have been reported in children (3-6). Bone lesion in children with ALL occurs in approximately 21% of leukemia at diagnosis. These lesions include transverse metaphyseal bands, osteolytic mottling and periosteal reactions.

ALL can rarely present with hypercalcemia, osteolytic lesion, and absence of circulating blasts (2). Here we report a case of ALL with the absence of circulating blasts presented with hypercalcemia.

## CASE REPORT

A 10 years old girl was admitted to our nephrology ward because of a history of left costovertebral pain, frequency, nausea, vomiting, anorexia and loss of weight without polydipsia, polyuria or constipation. The physical examination on admission showed mild hepatomegaly (2 cm below costal margin with a span

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**\* Corresponding Author:**

Z. Oloomi, Department of Pediatric Oncology, Imam Khomeini Hospital, School of Medicine, Medical Sciences/University of Tehran, Tehran, Iran  
Tel: +98 21 66927723  
Fax: +98 21 66927723  
E-mail: oloomi\_z@sina.tums.ac.ir

of 9 cm) and firm splenomegaly (2 cm below costal margin). Initial laboratory investigation revealed leukocyte count of  $7300 \text{ mm}^3$  (with 38% polymorphonuclear, 49% lymphocyte and 13% monocyte), hemoglobin level of 10.1 gr/dl, and platelet count of  $118 \times 10^3 \text{ mm}^3$ . The reticulocyte count was 0.8%.

In urine analysis, there were 1-2 red blood cells/HPF, and 30-35 white blood cells/HPF with negative culture. Serum calcium was 15.5 mg/dl, P = 2.9 mg/dl, BUN = 50 mg/dl and creatinine = 1.2 mg/dl, with normal electrolytes and normal liver function tests. Serum LDH was 2700 UI/L (normal range up to 500 UI/L). Serum parathormone was 10 µg/ml (normal range 10-65 µg/ml). Unfortunately we didn't have 25 dihydroxy-vitamin and calcitonin levels. The chest X-ray revealed no hilar or mediastinal mass. An ultrasound examination of the abdomen showed enlarged kidneys, with hyperechogenicity with no paraaortic nodes.

The hypercalcemia was initially treated with intravenous normal saline and furosemide for 3 days. Despite this treatment the hypercalcemia persisted and serum calcium level in the third day of treatment was 13.6 mg/dl. Total body plain radiographs identified bilateral small lytic lesions in the proximal site of both humerus. Suspecting neoplasia, a bone marrow aspiration from the iliac crest was performed, which revealed the presence of more than 80% of lymphoblasts with FAB-L2 morphology.

The neoplastic cells showed immunoeexpression for CD19, CD10, CD13, CD14 with HLA-DR positive consistent with B lineage ALL. Cytogenetic analysis on bone marrow aspiration was normal. Cerebrospinal fluid cytology revealed no leukemic cells (RBC = 0, WBC = 2 with 100% lymphocytes, glucose = 57 mg/dl).

After the diagnosis of ALL was made, induction chemotherapy was started according to the BFM protocol, and serum calcium level gradually normalized over the next 72 h to 9 mg/dl. At the time of this writing, the patient was in remission and had a good clinical condition, with normal serum calcium and no evidence of renal dysfunction.

We obtained informed consent from parents to publish details of their child illness.

## DISCUSSION

Hypercalcemia is a rare metabolic complication in childhood with an incidence of 0.4% in pediatric oncology patients (3), while it is a well recognized metabolic complication in adult malignancies, occurring in 5-10% of them (1). ALL accounts for approximately 50% of this metabolic complication in the pediatric age group (6) and in half of these patients, hypercalcemia is present at diagnosis.

As contrasted to patients with solid tumors and lymphomas who developed hypercalcemia later in the course of their diseases and their hypercalcemia is more resistant to treatment, children with acute leukemia are more likely to present with hypercalcemia and their hypercalcemia was more likely to respond to treatment (3). Hibi *et al.* reported an incidence 4.8% of leukemia presenting as hypercalcemia in children, that all of them had the pre-B-cell immunophenotype (6).

The underlying mechanism of hypercalcemia in lymphoproliferative disorders has been identified as increased osteoclastic activity mediated by cytokines produced by malignant cells, as tumor necrosis factor, interleukins 1 and 6 and parathormone-related protein (7). Another factor responsible for hypercalcemia can be decreased renal excretion of calcium due to decreased glomerular filtration, increased renal tubular absorption of calcium and increased renal phosphate loss. The osteoblastic activity is normal in these patients, so the scintigraphic examinations are often negative.

In children malignant hypercalcemia due to lymphoproliferative disorders necessitates urgent interventions to prevent severe renal, pancreatic, or cardiac complication. Serum calcium greater than 12 mg/dl can affect multiple organ systems, and levels exceeding 20 mg/ml can be fatal. Neuromuscular (lethargy, fatigue, hypotonia, stupor, coma), renal (polyuria, polydipsia), cardiovascular (bradycardia, arrhythmia) and gastrointestinal (nausea, vomiting, anorexia, constipation) symptoms dominate the clinical picture of malignant hypercalcemia (3, 4).

The initial treatment of hypercalcemia is intensive hydration and diuretics. If this treatment fails, corticosteroids may be useful. In our patient we

## ALL presenting as severe hypercalcemia

didn't administer corticosteroids for prevent of tumor lysis syndrome with its associated hyperphosphatemia, hyperuricemia and risk of nephrocalcinosis.

Recently bisphosphonates and in particular pamidronate has been used in childhood hypercalcemia (8, 9). Clinical response occurs in 16-48 h after administration and serum calcium levels usually normalize within 3-8 days (10, 11). In our patient we didn't administer bisphosphonates. Good control of the hypercalcemia was obtained after start of specific antileukemic treatment. The beneficial effects of this therapy on reducing the serum calcium concentration were likely due to the inhibition of the osteoclastic activity that was unregulated by tumor-derived osteoclast-activating factors.

In conclusion, malignant hypercalcemia represents an emergency in children and it may be complicate acute leukemia at diagnosis even without circulating blasts and pediatricians should be aware of this unusual presentation of ALL.

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