IJHOSCR

Case Report

International Journal of Hematology- Oncology and Stem Cell Research

Severe Hypercalcemia: A Rare and Unusual Presentation of Childhood Acute Lymphoblastic Leukemia

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Received: 2, Dec, 2013
Accepted: 16, Jan, 2014

ABSTRACT
Hypercalcemia in children is a medical emergency and often manifests as nonspecific symptoms such as nausea, vomiting, weight loss, and anorexia. Severe hypercalcemia is a rare complication of malignancy in children, while it can be seen in various types of malignant tumors. It is usually associated with significant morbidity and may be severe enough to threaten life. Incidence of hypercalcemia in hematopoietic malignancies including acute lymphoblastic leukemia (ALL) is very rare and unusual, especially as the initial manifestation of the disease. In this paper a 6-year-old boy who had severe hypercalcemia and gastrointestinal symptoms before the onset of common and usual manifestations of ALL is introduced.

KEY WORDS: Acute lymphoblastic leukemia, Hypercalcemia, Children

INTRODUCTION

Acute lymphoblastic leukemia (ALL), the most common malignancy in children, manifests with pallor, hepatosplenomegaly, lymphadenopathy, fever, bone pain, and bleeding. Hypercalcemia is potentially a life-threatening metabolic disorder and is often associated with nonspecific gastrointestinal symptoms such as nausea, vomiting, anorexia, constipation, and weight loss. This disorder can be seen in the course of many childhood cancers, but rarely in children with ALL at disease occurrence. Given that most patients with childhood ALL who present with hypercalcemia at diagnosis have nonspecific symptoms, diagnosis and treatment are delayed in these patients.[1, 2] Here we introduce a 6-year-old child who showed severe hypercalcemia and gastrointestinal symptoms before the occurrence of common and usual signs and symptoms of ALL.

CASE REPORT

The patient is a 6-year-old boy who is referred to our hospital with complaints of fever, malaise, anorexia, nausea, and vomiting from 4 weeks ago. During this period, the patient had lost 7 kg and his nausea, vomiting, and anorexia had gradually worsened. Before referral to us, he had several referrals as outpatients and two hospitalizations with no definite diagnosis of his illness. The physical examination showed only lethargy and pallor and no other signs including lymphadenopathy and hepatosplenomegaly.

Initial laboratory studies were as follows: Na: 141 mmol/L, K: 3.6mmol/L, BUN: 18, Cr: 0.8mg/dl, Ca: 15.8mg/dl, P: 2.8mg/dl, uric acid: 5.8 mg/dl, LDH: 587 U/L, Mg: 1.4mg/dl, Alkaline phosphatase: 305U/L, Alb: 4gr/dl. Complete blood count included: WBC: 7.4×10^9 /L (lymphocyte: 72%, PMN: 26%), HB: 7.1gr/dl, PLT: 90×10^9 /L. Arterial blood gas analysis was as follows: PH: 7.47, PCO2: 31mmHg, HCO3: 22 mEq/L.

Blood count was normal 16 days prior to our visit. In peripheral blood smear no other abnormal point was seen except microcytic anemia, and mild thrombocytopenia. Chest X-ray was normal. In abdominal ultrasound, liver and spleen size were normal and there was sand in inferior pole of right kidney. Despite severe hypercalcemia, there were no significant electrocardiographic changes. The corrected QT interval (QTc) was in the normal range and echocardiography was normal. Serum levels of PTH and 1,25-(OH)2 Vitamin D were 7 pg/ml (10-65 pg/ml) and 15 pg/ml (20-70 pg/ml), respectively, but it was impossible to measure PTHrP. Bone marrow aspiration was performed for the patient due to anemia, thrombocytopenia, prolonged fever, and weight loss. Bone marrow smears showed ALL with L1 morphology. Flowcytometry of bone marrow was also consistent with early pre B-ALL phenotype. Cytogenetic analysis of bone marrow was normal and showed 46, XY karyotype. Bone marrow samples analysis for t (9; 22), t (12; 21), t (1; 19), and t (4; 11) using PCR method were negative.

Patient was hospitalized in pediatric intensive care unit for treatment and close monitoring of severe hypercalcemia. Aggressive hydration with normal saline was started with two times of the maintenance. Pamidronate 1 mg/kg IV infusion over 4 hours and furosemide 1 mg/kg IV every 6 hours was started. After 12 hours of treatment onset, regarding the serum calcium level increment from 15.8 to 17 mg/dl, dexamethasone (2 mg every 12 hours) was added to the previous treatment. Since serum calcium level was 16 mg/dl, 36 hours after treatment, the patient underwent emergency hemodialysis, and then calcium level became normal. Pamidronate and furosemide were discontinued and regarding the diagnosis of ALL, the patient was undergone chemotherapy protocol ALL IC-BFM 2002. Dexamethasone was continued and calcium remained within normal limits and the patient's clinical symptoms, including nausea, vomiting, weakness and lethargy resolved. Bone marrow aspiration on day 15 showed complete remission with less than 5% blasts (M1 marrow). Chemotherapy was continued for 24 months and the patient is now in complete remission, 25 months after treatment discontinuation.

DISCUSSION

Compared to adults, hypercalcemia of malignancy is rare in children, and its overall incidence at different stages of the disease is 0.4%-1.3%.[1-3] In adult malignancies, unlike children, the incidence of hypercalcemia during the course of the disease is 20%-30%.[4] Hypercalcemia of malignancy in children has been reported in rhabdomyosarcoma, hepatoblastoma, Hodgkin and non-Hodgkin's lymphoma, brain tumors, neuroblastoma, angiosarcoma, acute lymphoblastic and myeloid leukemia.[2] Hypercalcemia is seen more in ALL than myeloid leukemia. These children are usually older and do not have blasts in smear of peripheral blood.[5] In the largest series reported from St Jude Children's Research Hospital, only 10 from 2816 children with lymphohematopoitic malignancy had ALL-induced hypercalcemia, of them only 7 had hypercalcemia at diagnosis.[2] The most common cause of hypercalcemia in paraneoplastic syndromes is ectopic production of hormone with similar effects of parathyroid hormone, which increases bone resorption by osteoclasts, increases renal reabsorption of calcium, and increases renal excretion of phosphate. Unlike PTHrP or other cytokines such as TNF and IL6 which increase in these diseases, PTH rarely increases.[1,5,7] In diseases such as Burkitt's lymphoma and multiple myeloma, hypercalcemia is usually due to increased activity of osteoclasts. Hypercalcemia symptoms are nonspecific and if left untreated may lead to cardiac arrhythmias, severe hypertension, renal failure, acidosis, dehydration, and coma.[5, 8]

Short-term treatment of hypercalcemia includes increased renal clearance and inhibition of bone resorption by osteoclasts and long-term treatment is to find and treat the underlying disease. Intense hydration with normal saline and furosemide are effective in increasing renal clearance of calcium. To

inhibit the activity of osteoclasts and bone resorption, bisphosphonates can be used. Calcitonin is also effective in the treatment of hypercalcemia. Other treatments such as mithramycin, gallium nitrate, and hemodialysis are effective in refractory cases. Calcium-containing medications should be discontinued and calcium-free diet is recommended. In hypercalcemia caused by lymphoproliferative diseases, prednisone is effective in the treatment of the underlying disease and hypercalcemia.[5, 6, 9, 10]

Except for sand presence in lower pole of the left kidney in this patient, there was no evidence of nephrocalcinosis and renal and heart function impairment. Hypercalcemia did not respond to primary treatment including vigorous hydration with normal saline, furosemide and pamidronate. Regarding the confirmation of ALL diagnosis, dexamethasone was also started and serum calcium slightly decreased, but regarding severe hypercalcemia and being symptomatic, the patient underwent hemodialysis and 4 hours later serum calcium level was decreased to 11 mg/dl. Only dexamethasone was continued after hemodialysis and patient calcium never exceed the normal limit. Although hypercalcemia was corrected after hemodialysis but remaining of serum calcium level in the normal range was achieved after dialysis and controlling of the underlying disease by corticosteroids.

The purpose of introducing of this patient is the rarity of hypercalcemia as the initial manifestation of childhood ALL and also to increase the awareness and attitudes of physicians in this field. Given the nonspecific symptoms of hypercalcemia, it is recommended to measure serum calcium in similar cases. In addition, early treatment of leukemia as the key element of treatment helps to quickly correct the hypercalcemia along with other therapies.

Conflict of interest

The authors declare no conflict of interest.

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