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Case Report

Osteolytic Bone Lesions, Hypercalcemia, and Renal Failure: A Rare Presentation of Childhood Acute Lymphoblastic Leukemia

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Abstract

Introduction: Pediatric acute lymphoblastic leukemia (ALL) rarely presents with hypercalcemia and diffuse osteolytic lesions. **Presentation of Case:** We report the case of a 17 year-old male with hypercalcemia, thrombocytopenia, and renal failure. Skeletal x-rays showed extensive osteolytic lesions. Pamidronate was used for treatment of hypercalcemia when calcitonin failed to maintain calcium levels within the normal range. Parathyroid hormone-related peptide (PTHrP) was not elevated. Bone marrow biopsy revealed B-precursor acute lymphoblastic leukemia. The patient failed two induction regimens but achieved remission after lymphoma-like chemotherapy. He continues to be in remission 7 years after double cord-blood transplantation.

Conclusions: The present case is used to explore the etiology and treatment of hypercalcemia associated with pediatric ALL, and to review the literature concerning the prognostic significance of multiple osteolytic lesions in a pediatric leukemia patient.

Keywords: Acute lymphoblastic leukemia; Hypercalcemia; Osteolytic bone lesions

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Introduction

Hypercalcemia is rare at diagnosis of childhood acute lymphoblastic leukemia (ALL) [1-3].The mechanism of ALL-induced hypercalcemia and osteolytic lesions is unclear, but is most likely related to the production of a factor by the tumor cells that activates osteoclasts. Parathyroid hormone-related peptide (PTHrP) is the most commonly described "osteoclast activating factor." The effect of skeletal lesions on prognosis is unclear. Several retrospective studies reported a better outcome in pediatric ALL patients with skeletal lesions, while other studies reported no prognostic effect or even a worse outcome.

Case Report

A seventeen year-old, previously healthy, male presented with complaints of nocturia, malaise, constipation, and vomiting. On physical exam, the patient had minimal tenderness to palpation of the left paraspinous muscles in the thoracic region and mild mid-epigastric tenderness but no lymphadenopathy or hepatosplenomegaly.

Table 1 Laboratory Data from Hospital Day 1 and Hospital Day 11

	Hospital Day 1		Hospital Day 11		Normal Range
Calcium	4.1	(H)	1.3	(L)	(2.1-2.6 mmol/L)
Blood urea nitrogen	24	(H)	14	(H)	(2.1-8.6 mmol/L)
Creatinine	407	(H)	115		(35-115 μmol/L)
Phosphorus	2.2	(H)	0.7	(L)	(1-1.6 mmol/L)
Magnesium	0.6		0.37	(L)	(0.53-0.86 mmol/L)
Albumin	47		30	(L)	(33-50 g/L)
Alkaline phosphatase	182		69	(L)	(80-250 U/L)
Lactate dehydrogenase	131		—		(99-207 U/L)
Uric acid	577	(H)	149		(119-327 μmol/L)
Hemoglobin	158		96	(L)	(125-161 g/L)
White blood cell count	6.4		5.6		(4.5-13 x 10^9/L)
Platelet count	80	(L)	44	(L)	(150-450 x 10^9/L)

H= high, L= low

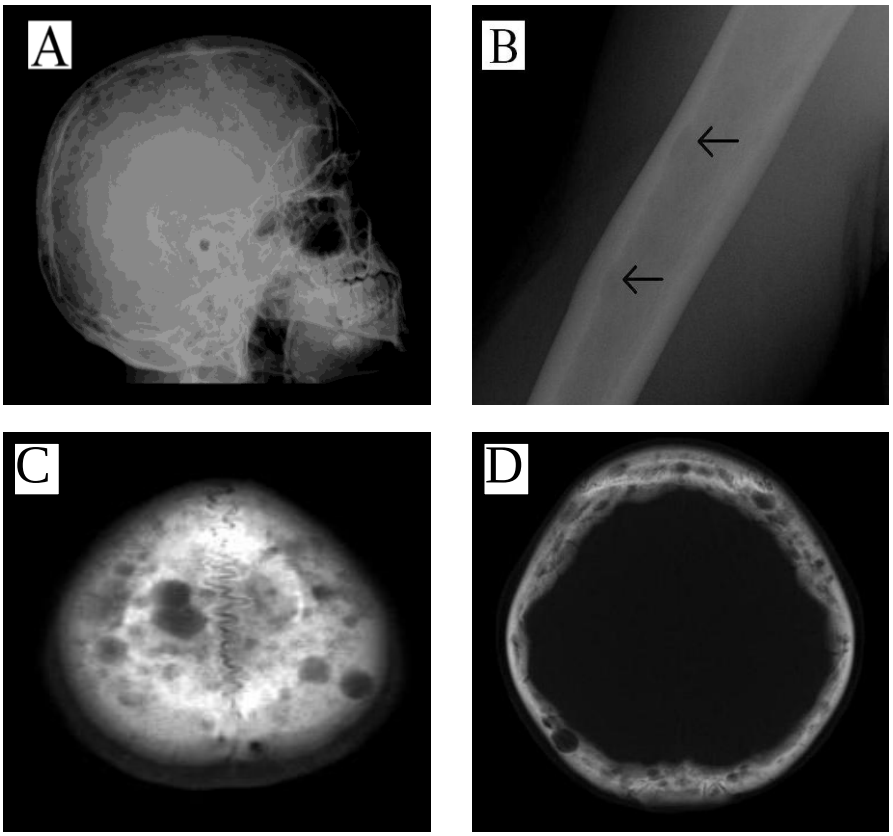
Initial laboratory evaluation showed elevated calcium (4.1 mmol/L) and phosphorus (2.2 mmol/L) with normal albumin and alkaline phosphatase. Blood urea nitrogen (24 mmol/L) and creatinine (407 mmol/L) were elevated. Uric acid (577 μmol/L) was elevated with normal LDH (Table 1). The patient had thrombocytopenia (80 $x10^9$/L), with a normal hemoglobin and normal white blood count and differential with no circulating blasts.

Hypercalcemia investigations revealed a normal 25-hydroxyvitamin D with low 1, 25-dihydroxyvitamin D (< 26 pmol/L) and below-normal intact parathyroid hormone (< 10 ng/L). Parathyroid hormone-related peptide (PTHrP) was not elevated (0.2 pmol/L - reference <2.0 pmol/L). Macrophage colony-stimulating factor (M-CSF) was normal (711.4 pg/ml - range 253-1715 pg/ml from 40 normal samples tested). Serum and urine protein electrophoresis, thyroid-stimulating hormone, and liver function tests were within normal limits. Antibodies to HTLV 1 and 2 were negative.

Skeletal survey revealed extensive lytic lesions involving the skull, pelvis, inferior ribs, proximal humeri, and proximal femora (Fig. 1. A-B). A bone scan revealed pathologic fractures in a lower right rib and the T8 vertebra, but otherwise underestimated the extent of

bony involvement. A head, chest, and abdominal CT scan confirmed numerous osteolytic lesions (Fig. 1.C-D). The osteolytic lesions of the calvarium were confined to the marrow space and did not involve the inner or outer table. Radiographic findings suggested a disseminated infiltrating lesion involving the marrow space. There was no periosteal reaction of the long bones or metaphyseal bands as are sometimes seen in ALL. The radiologic differential diagnosis focused on histiocytosis, leukemia, or lymphoma.

Figure 1



Skeletal Survey
A. Lateral view of the skull showing "mottled" appearance.
B. Diaphysis of right right humerus from skeletal survey showing "scalloping" (arrows)
Computed Tomography
C. and D. Cuts through the calvarium showing "moth-eaten" appearance

Bone marrow aspiration and biopsy revealed densely packed marrow. Flow cytometry confirmed B-precursor acute lymphoblastic leukemia with aberrant expression of CD13. Standard cytogenetics with multi-colored fluorescent in situ hybridization (FISH) showed a hypodiploid karyotype with complex abnormalities including loss of chromosome 13 [-13], deletions of 6q [del(6)(q15q21)] and 12p [del(12)(p13)], and abnormal chromosomes 11 [add(11)(p15)] and 21 [idic(21)(q22)]. Interphase FISH studies showed no evidence of rearrangements involving BCR/ABL1 or MLL while ETV6/RUNX1 confirmed the 12p- and idic(21q) rearrangements. Cerebrospinal fluid (CSF) was negative for malignant cells.

The patient was initially treated with intravenous normal saline and oral allopurinol. Hydration therapy resulted in slight improvement of the hypercalcemia without significant improvement in renal function. Calcitonin, given on hospital days three through five, achieved only temporary improvement of calcium levels. Subsequently, intravenous pamidronate (0.9 mg/kg) was given on hospital day six with resultant normalization of serum calcium within 24 hours. Rasburicase was used on day three of hospitalization, with a resultant decrease in serum uric acid to < 6 μmol/L by day 4 (Fig. 2).

The patient's renal function improved significantly after resolution of hyperuricemia and continued to normalize as calcium declined (Table 1).

Methylprednisone was given on hospital day 4 (as

treatment for the hypercalcemia) followed by induction with vincristine, dexamethasone, daunorubicin, and PEG-asparaginase. The patient did not achieve a remission with this regimen. A subsequent re-induction attempt with etoposide, cyclophosphamide, high-dose methotrexate and vinblastine followed by consolidation with cyclophosphamide, 6-MP, and cytarabine also failed to induce a remission. Using a B-cell lymphoma chemotherapy backbone (cyclophosphamide, vinblastine, prednisone, doxorubicin, and high-dose methotrexate), a remission was demonstrated on both bone marrow aspiration and biopsy. This was followed by a consolidation regimen consisting of clofarabine and cytarabine. He underwent unrelated double cord blood transplantation and rapidly achieved 100% donor engraftment. The patient continues in remission 7 years after a bone marrow transplant with no renal abnormalities or skeletal complaints.

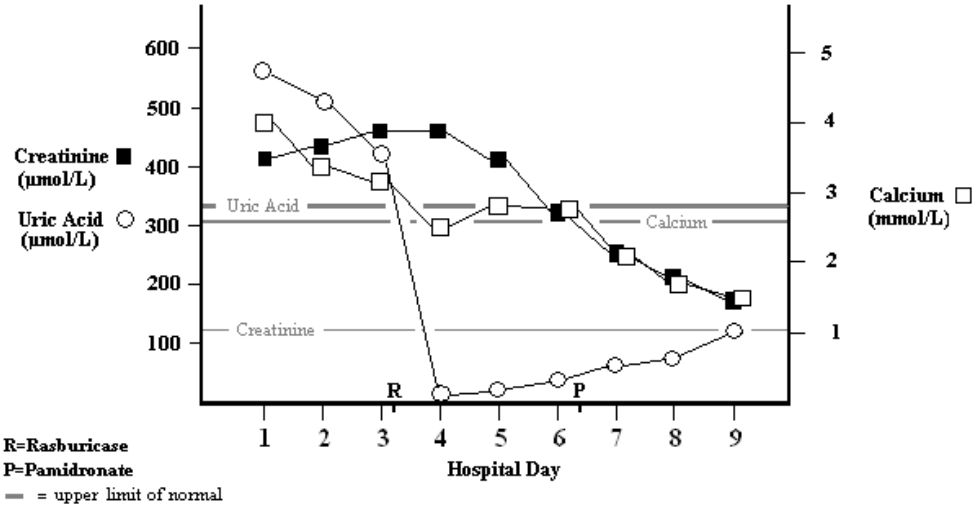


Figure 2: Laboratory Trend for Calcium, Creatinine, and Uric Acid

Discussion

Hypercalcemia is commonly seen with some adult hematologic malignancies such as multiple myeloma and adult T-cell lymphoma. However, hypercalcemia is not commonly associated with pediatric cancer. A large retrospective study that included more than 6,000 pediatric cancer patients (2,816 of whom had acute leukemia or lymphoma) reported a 0.4% incidence of hypercalcemia. In the group of patients with acute leukemia or lymphoma, the incidence of hypercalcemia at diagnosis was < 0.3%.1 Hibi et al. reported a higher incidence (4.8%) of hypercalcemia in a retrospective study that included 83 patients with early pre B-cell ALL[2] .

Tumor cells may induce hypercalcemia by directly invading bone or by producing factors that locally or systemically activate osteoclasts [3]. Some of the factors that have been implicated for their potential to induce hypercalcemia are included in Table 2.

Receptor activator of nuclear factor kappa-B ligand (RANKL), a protein encoded by gene tumor necrosis factor (ligand) superfamily, member 11 (TNFSF11), has been implicated as a possible mediator of hypercalcemia in cancer [5]. TNFSF11 is located in G-band region 13q14.11 [NC_000013.10 (43136872..43182149)] [9]. Interestingly, our patient and a patient reported by Shimonodan et. al.[10] have lost one chromosome 13. Their patient's homologue 13 appeared to have an interstitial deletion involving G-band region 13q14-q22, while our patient had a normal appearing homologue 13. They found no expression of RANKL by immunohistochemistry suggesting a homozygous deletion of TNFSF11 [10].We were not able to test for the expression of RANKL by immunohistochemistry. We employed FISH

analysis to determine if our patient had a microdeletion involving region 13q14 using two commercially available probes for RB1 and FKHR [locus FOXO1]. The FISH study showed no evidence of a deletion of either the RB1 or FKHR probes. But since TNFSF11 is proximal to both of these loci, a deletion of TNFSF11 may be present and not detectable by using either the RB1 or FKHR probe. To our knowledge RANKL overexpression has not been found in ALL.

Pamidronate proved very effective in reducing serum calcium levels in our patient. Pamidronate appears safe and effective in treating hypercalcemia associated with ALL [11].Dosing for pamidronate has been reported in a range of 0.5 to 2 mg/kg. Hypocalcemia and hypomagnesaemia can be a complication of the use of pamidronate.

Radiographic changes at leukemia diagnosis include osteopenia, radiolucent metaphyseal bands, periosteal new bone formation, and lytic and sclerotic lesions. Radiographic bone lesions at diagnosis have been reported in 41-70% of children with acute lymphoblastic leukemia [12]. We found 10 retrospective studies that evaluated the impact of bony lesions on the prognosis of pediatric leukemia [12-21]. Three retrospective studies published between 1985 and 1998 reported improved prognosis in patients with bone lesions [12-14].This is in contrast to three studies published between 1972 and 1996 which concluded that bony lesions have no impact on prognosis in pediatric patients with ALL [15-17]. Finally three studies published between 1976 and 1983 concluded that patients with three or more bony lesions have a worse prognosis than those patients without bony lesions [18-20].In addition, a study published in 1994 reported a worse prognosis in patients with 5 or more bony lesions compared to patients with one to four lesions.21 The discrepancies between these studies makes it difficult to draw conclusions about the prognostic impact of skeletal lesions in pediatric ALL. These studies included patients treated as early as 1963 and as late as 1995—a time period during which treatment and survival of pediatric patients with ALL changed dramatically. Skeletal lesions will remain important clues to help diagnose ALL. It is unclear if they will have a strong role in predicting prognosis.

Table 2 Factors Associated With Hypercalcemia of Malignancy

Factor	Reference Number
TNF-α, TNF-β	[4, 5]
IL-1α, IL-1β, IL-6	[4, 5]
TGF-α, TGF-β	[4]
PTHrP	[4, 5]
ectopic PTH	[3]
1,25 dihydroxyvitamin D	[4]
PG-E1, PG-E2	[6]
RANKL	[5]
MIP-1α	[7]
M-CSF	[8]
Lymphotoxin	[4]

TNF=tumor necrosis factor; IL=interleukin; TGF=transforming growth factor; PTHrP=parathyroid hormone-related peptide; PTH=parathyroid hormone; PG=prostaglandin; RANKL=receptor activator of nuclear factor κB, ligand/osteoprotegerin system; MIP=macrophage inflammatory protein; M-CSF=macrophage colony-stimulating factor

The present case has similar characteristics to pediatric patients with ALL and hypercalcemia described by Soni, (age 10-20 years, severe osteolytic bone lesions, lymphoblastic leukemia, and normal white cell count with rare or absent circulating blasts) [22].The patient's presentation with gastrointestinal symptoms is similar to other pediatric ALL patients with hypercalcemia and osteolytic lesions [22]. This is in contrast to most children with ALL who present commonly with fever, bleeding, malaise, and/or bone pain.

Conclusion

In conclusion, this case demonstrates the complex evaluation required for childhood ALL patients who present with hypercalcemia and osteolytic lesions. Further investigations are needed to clarify the molecular mechanism involved in ALL-associated

hypercalcemia

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