

Hypercalcemia in Acute Lymphoblastic Leukemia

An Overview

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Summary: Hypercalcemia usually results in nonspecific constitutional symptoms, although it can also manifest as a life threatening metabolic emergency. It is an uncommon albeit well recognized biochemical feature of childhood malignancies including acute leukemia. The pathogenesis of hypercalcemia and its implications in terms of long-term outcome are not yet fully understood. Most of the children presenting with acute lymphoblastic leukemia and hypercalcemia tend to be in older age groups and have an absence of blasts in the peripheral blood film. The chromosomal translocation 17;19 seems to be more frequent in children who present with hypercalcemia but the presence of hypercalcemia by itself does not seem to be closely linked to prognosis. Some of the less common immunophenotypes in the form of CD19 negativity and CD10 positivity have also been observed in hypercalcemic patients. In this study, we shall illustrate this clinical problem using the details of 2 patients with hematologic malignancy who were found to be hypercalcemic at presentation. We shall also review the literature with particular emphasis on the pathogenesis of hypercalcemia, its associations, and relationship to outcome.

Key Words: hypercalcemia, acute lymphoblastic leukemia

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Hypercalcemia is a relatively common biochemical feature of malignant disease in adults. Cancers commonly associated with raised calcium levels include breast cancer, multiple myeloma, non-Hodgkin lymphoma, adult T-cell leukemia, renal cell carcinoma, and non-small cell lung carcinoma. Although hypercalcemia may reflect direct skeletal involvement, humoral hypercalcemia of malignancy¹ was recognized in the 1930s as a syndrome in which hypercalcemia could occur in the absence of bony metastases. This is thought to be the case in around 5% to 20% of adult patients.^{1,2} In contrast, hypercalcemia is rarely seen in childhood malignancies. The solid tumors known to be associated with hypercalcemia in this age group include rhabdomyosarcoma,^{2,3} hepatoblastoma,

Hodgkin disease, non-Hodgkin lymphoma, brain tumors, and neuroblastomas.^{4,5} Hypercalcemia is reported to occur more commonly in acute lymphoblastic leukemia (ALL) as compared with acute myeloblastic leukemia⁶ and responds more readily to therapy in the leukemias as compared with solid tumors.

MECHANISMS RESULTING IN HYPERCALCEMIA

Hypercalcemia in patients with malignancy may arise because of localized bony destruction by cancer cells, altered osteoclastic activity under the influence of factors secreted by the cancer cells, or the increased production of 1,25-dihydroxyvitamin D, parathormone (PTH), or parathyroid hormone related protein (PTHrP).⁷ Hypercalcemia (serum levels ≥ 11.5 mg/dL or 2.9 mmol/L) usually results in nonspecific symptoms such as malaise, fatigue, polyuria, vomiting, abdominal pain, constipation, decreased renal function, and hypertension. The more life threatening manifestations include cardiac arrhythmias, renal failure, acidosis, severe hypertension, seizures, dehydration, and coma.^{7,8} Medications that may exacerbate hypercalcemia of malignancy include thiazide diuretics, oral contraceptives, and antacids containing calcium carbonate and lithium.

INVESTIGATIONS AT PRESENTATION

In addition to routine investigations (serum ionized calcium, phosphate, alkaline phosphatase, sodium, potassium, urea, creatinine total protein, and albumin levels) serum PTH and PTHrP, serum vitamin D metabolites, a skeletal survey, and isotope bone scan are usually appropriate.

MANAGEMENT

A number of strategies can be used to increase the renal clearance of calcium and inhibit osteoclastic bone resorption.^{2,6,7} These include:

- (i) Hydration with normal saline (up to 20 mL/kg hourly in the first instance).
- (ii) Augmentation of calciuresis with furosemide (2 mg/kg may be given every 4 h). Forced diuresis may require monitoring of intravascular volume as well as serum and urinary electrolytes.
- (iii) Administration of bisphosphonates: bisphosphonates block dissolution of the mineral component of bone and inhibit osteoclastic activity by inducing apoptosis of osteoclasts. A clinical response is usually observed within 12 to 48 hours and serum calcium levels normalize within 3 to 7 days. Bisphosphonates have a sustained effect on hypercalcemia. Intravenous therapy is the preferred route of administration and an appropriate starting dose of pamidronate in children is 0.5 to 1 mg/kg infused over 4 hours.

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- (iv) Calcitonin therapy: calcitonin inhibits osteoclastic bone resorption and enhances calcium excretion in urine. A decrease in serum calcium is seen within a few hours of administration but in contrast to bisphosphonate, lasts for a matter of days because of evolving resistance.

THE CLINICAL CONTEXT

We now describe 2 cases of ALL with hypercalcemia seen in our department over the last decade to highlight the clinical aspects of this problem and to provide background for further discussion.

Case 1

A 9-year-old boy diagnosed as neurofibromatosis type I at the age of 2 years, presented with symptoms of nausea and vomiting, painful ankles, dizziness, and excessive sleepiness for a period of 2 weeks. He also had a short, 2 days history of polydipsia and polyuria. On admission, he was mildly dehydrated with a blood pressure of 130/90 mm Hg. He had features of neurofibromatosis type I but his systemic examination was normal. His investigations revealed a calcium of 4.74 mmol/L (reference range 2.12 to 2.6 mmol/L), phosphate 1.26 mmol/L (0.88 to 1.44 mmol/L), sodium 139 mmol/L (reference range 135 to 145 mmol/L), glucose 7.1 mmol/L, alkaline phosphatase 200 μ /L (reference range 40 to 200 μ /L), creatinine 11 (reference range 7 to 11 mmol/L), and a suppressed PTH that was less than 5 ng/mL. Thyroxine concentrations (free T3 and free T4) were normal. His hemoglobin was 17 g/dL, white cell count 3.4×10^9 /L with the peripheral blood film showing a leukoerythroblastic picture. His chest radiograph was normal. An abdominal ultrasound showed enlarged kidneys but no discrete mass. Radiographs of his long bone suggested demineralization. In view of the leukoerythroblastic picture on his peripheral blood film a bone marrow examination was performed. This was consistent with a diagnosis of ALL (L1). CD10 and CD19 antigen expression were positive. He received intravenous fluids and pamidronate, which normalized his calcium. He was treated for ALL as per the Medical Research Council ALL 97/99 protocol and completed therapy in September 2002. Unfortunately, he relapsed 3 months after completion of chemotherapy. Bone marrow assessment at the time of relapse demonstrated a 9p deletion, which had not been present at initial diagnosis. He did not have hypercalcemia when he relapsed. He was started on chemotherapy and underwent bone marrow transplantation. Unfortunately, he had severe graft versus host disease and died within 100 days of the transplant.

Case 2

An 8-year-old boy presented with pain in his thoracolumbar area for a period of 3 months, maximal in the morning. This was initially relieved with paracetamol, but worsened over the 3 weeks before presentation to our hospital. There were no neurologic, bowel, or bladder symptoms. Other symptoms included poor appetite for 3 weeks and occasional right thigh pain. His maternal grandmother and her sister had developed bowel cancer. Examination revealed a comfortable well looking child. He had mild tenderness around the thoracolumbar junction as well as mild flexion at hips and knees when walking. Radiographs showed osteopenia and scalloping of the lower lumbar bodies, with anterior wedging of T7 and T9

vertebral bodies. The dual energy X ray absorptiometry scan showed a bone mineral density, which was greater than 3 SDs below the mean for age. His bone scan showed isotope uptake at T9 and a magnetic resonance imaging demonstrated an abnormal vertebral shape, but with no evidence of an infiltrative process. The plasma calcium was 3.06 mmol/L (reference range 2.12 to 2.6 mmol/L), the ionized fraction being 1.54 mmol/L (1.19 to 1.37 mmol/L), PTH was < 2 ng/mL, phosphate 1.69 mmol/L (0.8 to 1.44 mmol/L), total protein 74 g/L (reference range 58 to 78 g/L) with an albumin fraction of 45 g/L (reference range 34 to 50 g/L); magnesium of 0.82 mmol/L (reference range 0.8 to 1.4 mmol/L), alkaline phosphatase 177 U/L (reference range 40 to 200 U/L), and alkaline transaminase of 16 U/L (reference range 0 to 45 U/L). The initial diagnosis considered was idiopathic juvenile osteoporosis. His hemoglobin was 11.7 g/dL, white cells 31.3×10^9 /L, neutrophils 24.9×10^9 /L, and the peripheral film showed a mild shift to the left with a platelet count of 90×10^9 /L. He underwent a bone marrow examination, which was consistent with a diagnosis of ALL. Cytogenetic analysis demonstrated Philadelphia chromosome positivity. Chemotherapy was commenced as per the Medical Research Council ALL 2003 protocol. His hypercalcemia responded to pamidronate. As he was Philadelphia chromosome positive, he underwent bone marrow transplantation in first remission in February 2007 and has been well after the transplantation.

DISCUSSION

Both of the children had interesting features at presentation. One had classical symptoms of hypercalcemia and the second child presented with vertebral collapse. Both were in an older age group and neither had classical features of leukemia nor blasts in the peripheral blood film.

Many instances of hypercalcemia in hematologic malignancies in childhood are in the form of case reports. However, the incidence of hypercalcemia in leukemia seems to be around 0.6% to 4.8%. The largest series reported from St Jude highlighted 11 of 2816 children with leukemia who had hypercalcemia.² Ten children had ALL and 1 had acute myeloblastic leukemia. Seven of the 10 children with ALL had hypercalcemia at presentation. More recently a group in Japan reported 25 children with ALL presenting over a 15-year period, all of whom had hypercalcemia at presentation.⁹ Approximately 500 children are estimated to develop ALL per year in Japan.⁹

There are 2 principle mechanisms for the hypercalcemia of malignancy in children. The first is localized bone destruction by invasive cancer cells. This destructive process involves the local release of a range of cytokines.^{1,7,10} The second mechanism involves osteoclastic bone resorption after the release of humoral derived factors from tumor cells. These factors include PTHrP and bone resorption stimulating factors such as tumor necrosis factor (TNF)- α and β , transforming growth factor β , interleukin 1 β , interleukin 6, and vitamin D sterols.^{11,12}

Proinflammatory cytokines are thought to promote bone resorption by stimulating proliferation and maturation of osteoclasts through their interaction with receptor activator of nuclear factor κ B ligand (RANKL) which induces the differentiation of hematopoietic precursor cells into osteoclasts.¹² Cytokines induce the expression of RANKL by osteoblasts or stromal cells and activate

osteoclasts through the binding of RANKL to RANK on the osteoclast cell surface.

PTHrP has been considered as the major mediator of hypercalcemia in malignancies and has been reported to have a similar activity to PTH. PTHrP was initially demonstrated in lung cancer and was found to share a high degree of sequence homology with PTH.¹³ However, immunologic differences exist between the molecules and there are differences in tissue binding. PTHrP may result in hypercalcemia by, firstly, altering renal tubular calcium and phosphate transport, secondly by increasing nephrogenous cyclic adenosine monophosphate and 1,25-dihydroxyvitamin D production, and thirdly, by stimulating osteoclasts which then increase bone resorption.¹⁴ In a recent study, 11 of 21 children with ALL and hypercalcemia had PTHrP mediated hypercalcemia⁹ suggesting that it was the most important mechanism resulting in hypercalcemia in childhood ALL. In ALL it is thought that lymphoblasts produce PTHrP directly.^{9,11,12,15}

Certain clinical characteristics are of note in children with ALL who present with hypercalcemia (Table 1). The median age of the children at presentation on available data is 8 years with a SD of 4.05 years. Most patients do not have a strikingly deranged blood count and absence of blasts in the peripheral blood film is not uncommon. The main symptoms seen are emesis, lethargy, and bone pain. Patients who did not have an abnormal full blood count at presentation typically took some time for a diagnosis to be established.

Inukai and coworkers found that 5 of their 22 patients had t(17;19) on cytogenetic analysis and all of these 5 children relapsed. Three of the 5 had definite evidence of PTHrP dependent hypercalcemia. t(17;19) is seen in 1% of B precursor ALL children and this translocation has also been associated with disseminated intravascular coagulation and hypercalcemia.²² It affects the band p13.3 of chromosome 19 which involves the E2A gene. This translocation results in a chimeric transcript that contains sequences of the E2A gene fused with those of hepatic leukemia factor gene (HLF) on chromosome 17. This gene-

rates the E2A-HLF fusion transcription factor. The E2A-HLF fusion protein protects cells from apoptosis owing to growth factor deprivation and these cases have been associated with a poor prognosis.^{23,24} Of the 10 children with hypercalcemia reported from St Jude, 2 showed a t(17;19) on cytogenetic analysis. No other specific cytogenetic abnormality seems to feature in these children and of note is that there is no association with abnormalities of the 11p and 12p regions where the gene for PTH and PTHrP is located. Cytogenetics in our index patients had a 9p deletion at relapse in the first case, whereas the second child was Philadelphia chromosome positive. Studies have shown that patients with 9p abnormalities (translocation or deletion) have an inferior outcome (4 y event-free survival: 50% vs. 75%).^{25,26} Allelotype analysis has shown 68% patients to have loss of heterozygosity on at least 1 chromosomal arm at relapse with the most frequent being on chromosome arm 9p.²⁷ The second child had Philadelphia chromosome positivity; Philadelphia chromosome is seen in 3% to 5% of children of ALL and is also associated with a poor prognosis.²⁸

Interestingly, there have been reports of children with hypercalcemia who were precursor B ALL with "odd" features.^{20,29} These children were immunophenotype positive for CD10, CD34, and human leukocyte antigen-DR but negative for CD19. In contrast to the age of most children reported, these 3 patients were young (9 mo, 2 y, and 2 y). All had PTHrP independent hypercalcemia with 2 having a marked increase in the serum TNF- α and IL-6. (This was not assessed in the third child reported). The authors suspected that TNF- α and IL-6 had caused osteoclastic bone resorption resulting in hypercalcemia with disseminated osteolysis.²⁹ IL-6 and TNF- α promote osteoclastic bone resorption but PTHrP independent hypercalcemia with raised proinflammatory cytokines is rare in children. The authors commented on the possible relationship/relevance of CD19 negativity and PTHrP independent hypercalcemia in childhood ALL.²⁹

An obvious question is whether hypercalcemia affects the outcome in ALL. The largest series of 22 children with

TABLE 1. Pediatric ALL With Hypercalcemia at Presentation

Report	Age	Blood Counts and Peripheral Blood Film	Genetics	Outcome
Inukai et al ⁹	11 of 22 patients > 10 y	No blasts in 8 of 22 patients	t(17;19) in 5 patients	Outcome same as in other children with ALL
Soni ¹⁰	12 y	No blasts	Not described	All with t(17;19) relapsed
Lankish et al ¹⁶	9 y	No blasts	Not described	Not known
Buonumio et al ¹⁷	9 y	No blasts	Normal karyotype	Well; off treatment
McKay and Furman ²	10 cases (7 at presentation)	Not described	t(17;19) in 2 patients	Alive 16 mo after diagnosis
Turker et al ¹⁸	Not known	Slightly increased WBC	Not described	4 alive (13 mo to 6 y)
Boudailliez et al ¹⁹	10 y	Blasts +	Not known	3 dead
Sultan et al ²⁰	9 mo	Normal	Normal	Not known
Mathur et al ²¹	8 y	Blasts +	Not described	Not known
Royal Victoria Infirmary, Newcastle upon Tyne, UK	(1) 9 y (2) 8 y	(1) Leukoerythroblastic film (2) Normal counts No blasts in both	(1) Normal (2) Philadelphia chromosome +	Alive 16 mo after diagnosis
				Remission at time of print
				(1) Died after BMT
				(2) Underwent BMT

+ indicates positive; ALL, acute lymphoblastic leukemia; BMT, bone marrow transplantation; t, translocation; WBC, white blood cells.

ALL who presented with hypercalcemia has been recently reported.⁸ They found the event-free survival in children with hypercalcemia at presentation to be similar to those who did not have hypercalcemia suggesting that hypercalcemia at presentation is not necessarily a poor prognostic factor. However, 5 of the reported children had *t*(17;19) (which per se is a poor prognostic factor) and it was felt that the presence of hypercalcemia at presentation might be more common in ALL *t*(17;19). Review of other reported cases does not seem to indicate a poor prognosis with hypercalcemia despite the possible link with tumor bulk.

CONCLUSIONS

A number of pathogenic mechanisms may be involved in the evolution of hypercalcemia in young patients with malignancy. The same mechanisms may operate in the subgroup of children with ALL and hypercalcemia. Most ALL children with hypercalcemia seem to be in the older age group whereas some of the younger ALL children with hypercalcemia have had CD19 negative B precursor ALL and the relevance of this needs further investigation. The *t*(17;19) is frequently seen in patients with hypercalcemia and it seems that hypercalcemia is PTHrP mediated in such cases. No other cytogenetic abnormality has a clear association with hypercalcemia in ALL and hypercalcemia by itself does not seem to confer a poor prognosis.

REFERENCES

- Mundy GR, Ibbotson KJ, D'Souza SM, et al. The hypercalcemia of cancer. Clinical implications and pathogenic mechanisms. *N Engl J Med*. 1984;310:1718–1727.
- McKay C, Furman WL. Hypercalcemia complicating childhood malignancies. *Cancer*. 1993;72:256–260.
- Kawasaki H, Takayama J, Nagasaki K, et al. Hypercalcemia in children with rhabdomyosarcoma. *J Pediatr Hematol Oncol*. 1998;20:327–329.
- Seymour JE, Gagel RE. Calcitriol: the major humoral mediator of hypercalcemia in Hodgkin's disease and non-Hodgkin's lymphomas. *Blood*. 1993;82:1383–1394.
- Leblanc A, Caillaud MI, Hartmann O, et al. Hypercalcemia preferentially occurs in unusual forms of childhood non-Hodgkin's lymphoma, rhabdomyosarcoma and Wilms' tumour. A study of 11 cases. *Cancer*. 1984;54:2132–2136.
- Body JJ, Bartl R, Burckhardt P, et al. Current use of bisphosphonates. *J Clin Oncol*. 1998;16:3890–3899.
- Rheingold SR, Lange BJ. Oncologic emergencies. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*. 5th ed. Philadelphia: Lippincott, Williams and Wilkins; 2006:1202–1230.
- Ribiero RC, Pui CH. Acute complications in childhood leukemias. In: Pui CH, ed. *Childhood Leukemias*. 1st ed. Cambridge: Cambridge University Press; 2000:443–462.
- Inukai T, Hirose K, Inaba T, et al. Hypercalcemia in childhood acute lymphoblastic leukemia: frequent implication of parathyroid hormone-related peptide and E2A-HLF from translocation 17;19. *Leukemia*. 2007;21:288–296.
- Soni PN. Hypercalcemia and multiple osteolytic lesions in childhood acute lymphoblastic leukemia. *Postgrad Med J*. 1993;69:483–485.
- Harutsumi M, Akazai A, Kitamura T, et al. A case of acute lymphoblastic leukemia accompanied with the production of parathyroid hormone-related protein. *Miner Electrolyte Metab*. 1995;21:171–176.
- Shimonodan H, Nagayama J, Nagatoshi Y, et al. Acute lymphocytic leukemia in adolescence with osteolytic lesions and hypercalcemia mediated by lymphoblast-producing parathyroid hormone-related peptide: a case report and review of the literature. *Pediatr Blood Cancer*. 2005;45:333–339.
- Suva LJ, Winslow GA, Wettenhall RE, et al. A parathyroid hormone related protein implicated in malignant hypercalcemia: cloning and expression. *Science*. 1987;237:893–896.
- Akatsu T, Takahashi N, Udagawa N, et al. Parathyroid hormone (PTH) related protein is a potent stimulator of osteoclast-like multinucleated cell formation to the same extent as PTH in mouse marrow cultures. *Endocrinology*. 1989;125:20–27.
- Jayaraman J, David R. Hypercalcemia as a presenting manifestation of leukemia: evidence of excessive PTH secretion. *J Pediatr*. 1977;90:609–610.
- Lankish P, Kramm CM, Hermesen D, et al. Hypercalcemia with nephrocalcinosis and impaired renal function due to increased parathyroid hormone secretion at onset of childhood acute lymphoblastic leukemia. *Leuk Lymphoma*. 2004;45:1695–1697.
- Buonumano PS, Ruggiero A, Piasha M, et al. A case of acute lymphoblastic leukemia presenting as severe hypercalcemia. *Paediatr Haematol Oncol*. 2004;21:475–479.
- Turker M, Oren H, Yilmaz S, et al. Unusual presentation of childhood acute lymphoblastic leukemia. A case presenting with hypercalcemia symptoms only. *J Pediatr Hematol Oncol*. 2004;26:116–117.
- Boudailliez BR, Pautard BJ, Sebert JL, et al. Leukemia associated hypercalcemia in a 10 year old boy: effectiveness of amino-hydroxypropylidene bisphosphonate. *Pediatr Nephrol*. 1990;4:510–511.
- Sultan I, Kravets JM, Lazarchik JU. CD19 negative precursor B acute lymphoblastic leukemia presenting with hypercalcemia. *Pediatr Blood Cancer*. 2004;43:66–69.
- Mathur M, Sykas JA, Saxena VR, et al. Treatment of acute lymphoblastic leukemia-induced extreme hypercalcemia with pamidronate and calcitonin. *Pediatr Crit Care Med*. 2003;4:252–255.
- Raimondi SC. Cytogenetics in acute leukemia. In: Pui CH, ed. *Childhood Leukemias*. 1st ed. Cambridge: Cambridge University Press; 2000:168–196.
- Matsunaga T, Inaba T, Matsui H et al. Regulation of annexin II by cytokine-initiated signaling pathways and E2A-HLF oncoprotein. *Blood*. 2004;103:3185–3191.
- Inukai T, Inaba T, Dang J, et al. TEF, an antiapoptotic bZIP transcription factor related to the oncogenic E2A-HLF chimera, inhibits cell growth by down-regulating expression of the common beta chain of cytokine receptors. *Blood*. 2005;105:4437–4444.
- Pollak C, Hagemeijer A. Abnormalities of the short arm of chromosome 9 with partial loss of material in hematological disorders. *Leukemia*. 1987;1:541–548.
- Murphy SB, Raimondi SC, Rivera GK, et al. Nonrandom abnormalities of chromosome 9p in childhood acute lymphoblastic leukemia: association with high risk clinical features. *Blood*. 1989;74:409–415.
- Takenchi S, Periu T, van Drogen JJ, et al. Allelotype analysis on relapsed childhood acute lymphoblastic leukemia. *Oncogene*. 2003;22:6970–6976.
- Crist W, Carroll A, Shuster J, et al. Philadelphia chromosome positive childhood acute lymphoblastic leukemia: clinical and cytogenetic characteristics and treatment outcome. A Pediatric Oncology Group study. *Blood*. 1990;76:489–494.
- Niizuma H, Fujii K, Sato A, et al. PTHrP independent hypercalcemia with increased proinflammatory cytokines and bone resorption in two children with CD19- negative precursor B acute lymphoblastic leukemia. *Pediatr Blood Cancer*. 2007;49:990–993.