

# Hypercalcemia in Pediatric Acute Megakaryocytic Leukemia

## Case Report and Review of the Literature

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**Summary:** Hypercalcemia has been described as a possible complication of many pediatric malignancies. Here, we report an 8-month-old non-Down syndrome infant with acute megakaryocytic leukemia and severe hypercalcemia at presentation. A review of the literature reveals that this is the first case of hypercalcemia complicating acute megakaryocytic leukemia reported in the pediatric literature. His initial workup, and the course of management and outcome, is described in detail. Though the etiology of this complication remains unclear, our experience suggests that early institution of chemotherapy along with supportive care is the best treatment for control of hypercalcemia.

**Key Words:** hypercalcemia, acute megakaryocytic leukemia, pediatric, pamidronate

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Hypercalcemia is becoming an increasingly recognized metabolic complication of pediatric malignancies. There have been several reports describing hematologic malignancies and solid tumors complicated by hypercalcemia. Also, there is an increasing awareness for the need for treatment protocols adapted to the pediatric age group.<sup>1–3</sup> Hypercalcemia complicating acute myeloid leukemia (AML) is well recognized in the adult population,<sup>4</sup> but there have been only a few reports of pediatric patients with AML developing hypercalcemia, and none with acute megakaryocytic leukemia (AMKL).<sup>1,4,5</sup> We describe an 8-month-old male with de novo acute megakaryoblastic leukemia with diffuse skeletal involvement and severe hypercalcemia at presentation.

### CASE REPORT

An 8-month-old male presented with 10 days history of fever and persistent crying. Physical examination was significant for high temperature (39°C), fussiness, pallor, petechiae, and oral thrush. There were no features of Down syndrome. The initial laboratory evaluation revealed a white blood cell count of 11,000/mm<sup>3</sup> (myelocytes 7%, bands 2%, neutrophils 25%, lymphocytes 62%, and monocytes 4%), hemoglobin 8.7 g/dL, and platelet count 17,000/mm<sup>3</sup>. His serum calcium was 13.6 mg/dL (normal 8 to

10.5 mg/dL), ionized calcium was 1.85 mM/L (normal 1.13 to 1.32 mM/L), phosphorus was 5.9 mg/dL (normal 2.5 to 5 mg/dL), and albumin was 3.5 g/dL (normal 3.2 to 5.7 g/dL). The urine calcium/creatinine ratio was 1.2 (95th percentile for age is 0.60). His peripheral blood smear showed blasts with L1 morphology. There were no electrocardiogram changes secondary to hypercalcemia. The bone marrow aspirate/biopsy revealed extensive bone marrow fibrosis with blasts; immune-histochemistry and flow cytometry were consistent with AMKL (negative for myeloperoxidase and focally positive periodic acid Schiff stain; CD45 dim myeloblast population expressing CD40, CD33, weak CD4, and platelet-associated antigens CD41+61, CD36, and CD9, respectively). Cytogenetic examination of blasts revealed 49-51, XY, +6, +del (9) (q22), add (15) (p11), +15, +19 [cp7]/46, XY [13]. There was no trisomy 21 or (1;22) translocation. There was no clinical suspicion of an underlying germline mutation.

A skeletal survey showed generalized osteopenia with mottled appearance of the calvarium, ribs, spine, and pelvic bones with destructive changes in the proximal humeri and proximal femurs (Fig. 1); and renal ultrasound showed evidence of early nephrocalcinosis. Additional investigations for the etiology of hypercalcemia revealed serum intact parathyroid hormone to be less than 3 pg/mL (normal 7 to 53 pg/mL), parathyroid hormone-related peptide to be 0.8 pmol/L (normal <1.1 pmol/L), 25-hydroxy vitamin D of 50 ng/mL (normal 20 to 57 ng/mL), and 1, 25 (OH)<sub>2</sub> vitamin D to be 12 pg/mL (normal 15 to 75 pg/mL).

The patient was admitted to the intensive care unit for monitoring and treatment of severe hypercalcemia (Fig. 2). Initial therapy consisted of intravenous fluids at twice the daily maintenance rate (200 mL/kg/d) and furosemide (1 mg/kg every 8 h intravenously) for management of hypercalcemia. However, as the hypercalcemia was refractory to furosemide, on hospital day 3, salmon calcitonin was started (2 units/kg subcutaneously every 12 hours and increased over 3 d to 8 units/kg every 6 h).

The serum calcium peaked at 17.8 mg/dL on the sixth day of presentation. The child was started on a 24-hour infusion of pamidronate (1 mg/kg) and chemotherapy as per the St Jude 2002 induction protocol (cytarabine/doxorubicin and etoposide). Twenty-four hours after finishing pamidronate infusion, serum calcium started to decrease. Hypocalcemia and hypophosphatemia resulted; intravenous calcium gluconate supplementation was required for 8 days. This was followed by a slight increase of serum calcium to 11.1 mg/dL before stabilizing. Bone marrow aspirate at the end of the first induction cycle revealed remission M1 marrow, negative for minimal residual disease. His calcium and vitamin D levels have remained normal and his x-rays have normalized. His intact parathyroid hormone level was not repeated.

The patient's hospital courses were complicated by deep vein thrombosis, typhilitis, catheter-related sepsis, and disseminated fungal infection. The child maintained complete remission for more than 2 years.

### DISCUSSION

The incidence of hypercalcemia that has been reported at presentation, during treatment, and during relapse in

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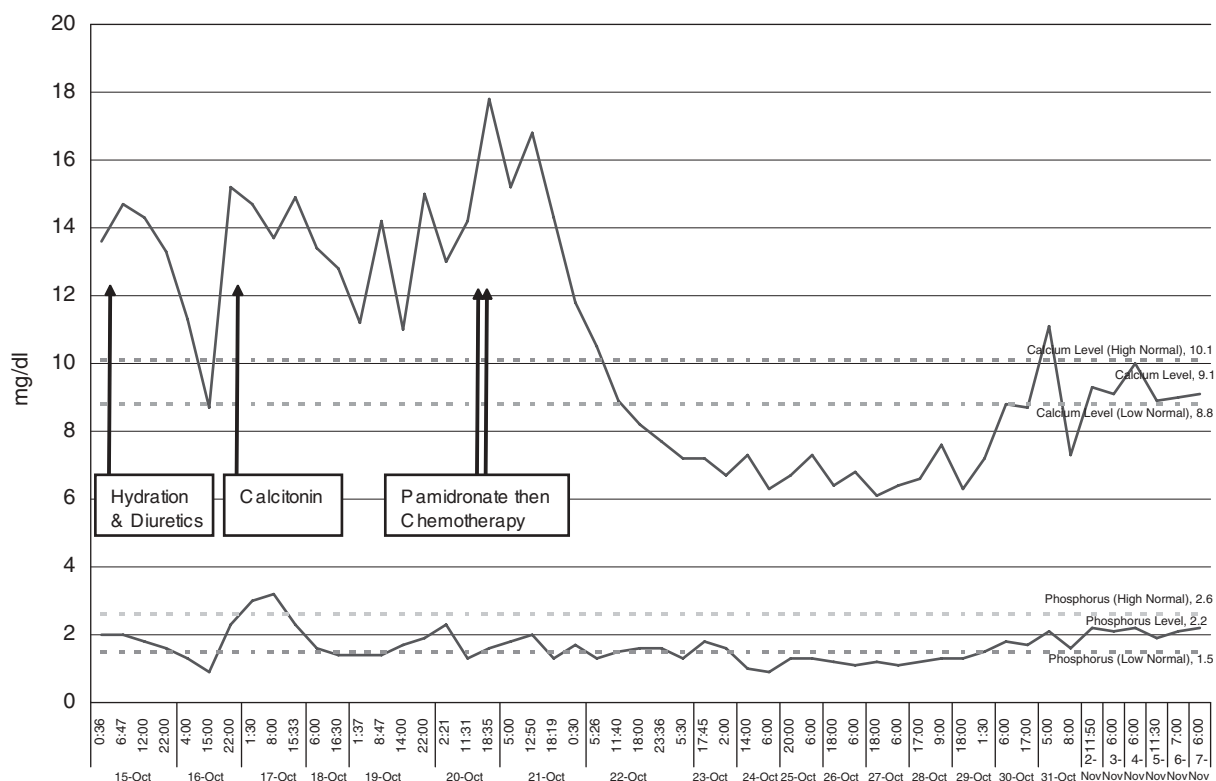
**FIGURE 1.** Bone changes. "Generalized osteopenia with mottled appearance of the calvarium, ribs, spine, and pelvic bones with destructive changes in the proximal humeri and proximal femurs."

childhood malignancies is 0.4% to 1.3%.<sup>1,2</sup> Most common malignancies associated with hypercalcemia include acute lymphoblastic leukemia and lymphoma, solid tumors rhabdomyosarcoma, neuroblastoma, and malignant rhabdoid tumors.<sup>1,3,6,7</sup> This is in contrast to the incidence of hypercalcemia of adult malignancies, where it is as high as 20% to 30% during the course of the disease.<sup>8</sup>

Of the hematologic malignancies with hypercalcemia, AML is less likely to be the cause. In the year 1983, Gewirtz et al<sup>4</sup> reviewed all case reports linking AML and hypercalcemia. Of the 10 cases reported, only 2 were in the pediatric age group. Our review of the English literature using PubMed search engine revealed reports of only 4 pediatric patients, a 14-month-old female with AML M5<sup>5</sup>; an 18-year-old female with AML M5<sup>1</sup>; a 13-year-old male with AML M3<sup>9</sup>; and a 14-year-old female with AML (unspecified).<sup>4</sup> None of the pediatric patients and only 1 adult reported<sup>10</sup> had AMKL.

The etiology of hypercalcemia in AML remains poorly defined. Abnormal parathyroid hormone production by myeloid cells, production of parathyroid hormone-related peptide, and elevated levels of 1, 25 (OH)<sub>2</sub> vitamin D have all been implicated.<sup>10</sup> None of those levels were elevated in our patient. Furthermore, the suppressed 1, 25 (OH)<sub>2</sub> vitamin D supports the lack of exogenous production of calcitriol as reported with other hematologic malignancies.<sup>11,12</sup> The suppressed 1, 25 (OH)<sub>2</sub> vitamin D is most possible owing to the hypercalcemia negative feedback inhibition of the renal 1- $\alpha$  hydroxylase activity.<sup>13</sup>

We attribute the hypercalcemia in our case to local osteolytic activity secondary to bony destruction from leukemic infiltrates that lead to calcium release into the extracellular space<sup>14</sup> and possible production of local



**FIGURE 2.** Time line for the management of hypercalcemia.

proinflammatory cytokines like tumor necrosis factor- $\alpha$ , interleukin-6, and prostaglandin E2 that have a stimulatory effect on osteolytic bone resorption.<sup>5,15</sup> Those values were not obtained in our case, which necessitates attention to the initial workup for hypercalcemia with cancer.

Our patient presented with significant hypercalcemia, myelofibrosis, and extensive diffuse skeletal involvement, when compared with other de novo AMKL patients with skeletal involvement. Skeletal lesions in AMKL have revealed in previous reports bilateral symmetric periosteal reaction, multiple osteolytic lesions, and pathologic fractures as the main findings.<sup>16–22</sup> Periosteal reaction involving the long bones of the lower limbs was prominent in more than 50% of patients. This is in contrast to the well-documented radiology of leukemia, where periosteal reaction represents (9% to 16%), is not usually marked, and is rare in isolation.<sup>17</sup> Most reported patients with AMKL and skeletal findings had associated myelofibrosis; all except 1 had de novo AMKL.<sup>22</sup> None of these previously reported patients reported, however, had hypercalcemia.

The non-Down syndrome patient described in this report developed AMKL lacking cytogenetic characteristics of acquired trisomy 21 or t (1;22).<sup>23,24</sup> These leukemic cells displayed a complex cytogenetic pattern with trisomies +6 and +19. Both have been reported to be associated with de novo AMKL.<sup>25–27</sup> Trisomy 15 is a rare finding that has been reported with different forms of hematologic malignancies, but none of the reports were associated with pediatric AMKL.<sup>28</sup> No other reports have suggested any association between the cytogenetic abnormality in this patient and hypercalcemia.

Untreated, hypercalcemia may result in cardiac arrhythmias, renal failure, severe hypertension, and coma. This patient had mild nephrocalcinosis on initial workup suggesting sustained calcium elevation with tissue deposition. There was no evidence of impaired renal function and no cardiac effect despite severe hypercalcemia (levels > 14 mg/dL).<sup>8</sup> The malignancy-associated hypercalcemia in this patient was refractory to aggressive hydration with normal saline and to furosemide to augment calciuresis. These measures are considered initial therapy toward the resolution of hypercalcemia.<sup>1</sup> Because of its lowering of serum calcium by inhibiting bone resorption, calcitonin therapy was used in this patient. Calcitonin, however, has short duration of action.<sup>29</sup> Pediatric experience using pamidronate is limited to case reports and series.<sup>2,30–32</sup> Studies have suggested the starting dose of 1 mg/kg,<sup>2,32</sup> with an initial response within 1 to 3 days and a maximum by 7 days. Kerdudo et al<sup>2</sup> reviewed 16 cases of pediatric cancer with hypercalcemia, 8 cases required bisphosphonate use. On the basis of their experience, and the limited reports in the literature, the use of pamidronate is recommended in the absence of correction of serum calcium after 24 hours of symptomatic management or in patients with severe hypercalcemia. Delayed effect may occur and monitoring for secondary hypocalcemia, hypophosphatemia, and hypomagnesemia for up to 2 weeks after administration is recommended. Infusion over several hours (up to 24h) may reduce the risk of renal toxicity (Lexi-comp). The rapid decline in serum calcium and serum phosphorus in our patient was attributed to the use of pamidronate infusion. However, ultimate control of hypercalcemia was gained by induction chemotherapy, by controlling the primary cause, the AMKL.

## CONCLUSIONS

We report the first case of malignant hypercalcemia in a pediatric patient with de novo AMKL with associated skeletal involvement. We reviewed the incidence of hypercalcemia in pediatric AMKL, associated skeletal findings, pathogenesis, and management. We feel that early initiation of chemotherapy is the ultimate control of hypercalcemia. We recommend the development of a registry for the childhood malignancy, risk factors, and tumor cytogenetics associated with hypercalcemia.

Most of the literature reviewing the treatment of hypercalcemia of malignancy<sup>33,34</sup> is based on the experiences in the adult population. With the increasing recognition of hypercalcemia as a complication of pediatric malignancies, the need for specific treatment protocols is clear.

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