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Acute Lymphoblastic Leukemia with Malignant Hypercalcemia: A Case Report

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Data Interpretation D
Manuscript Preparation E
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Patient: Female, 6
Final Diagnosis: Acute lymphoblastic leukemia
Symptoms: Abdominal pain • bloody diarrhea • malaise • vomiting
Medication: —
Clinical Procedure: Chemotherapy
Specialty: Oncology

Objective: Unusual clinical course

Background: Malignant hypercalcemia is a rare finding in the pediatric population, even more rare in hematological malignancies, such as leukemia.

Case Report: We present a case of a 6-year-old female patient who was diagnosed with acute lymphoblastic leukemia, with secondary hypercalcemia. She started chemotherapy following the IC-BFM ALL2002 protocol with simultaneous calcitonin, diuretics and aggressive hydration for hypercalcemia, and went into complete remission after the induction therapy. After 4 months of chemotherapy, she was diagnosed with relapse associated again with malignant hypercalcemia, and underwent chemotherapy with the relapse protocol. There was no response after the first 2 cycles, so we decided to start her on clofarabine. Due to the severe hypercalcemia and consecutive osteolysis, she developed several bone fractures and needed gypsum immobilization. We started her again on calcitonin, but she developed severe adverse reactions, so we found it necessary to start bisphosphonates, first zoledronic acid intravenously, and afterwards clodronate orally. Consolidation of bone fractures was achieved, but due to prolonged immobilization she developed bedsores, superinfected with *Lichtheimia corymbifera*. We started posaconazole orally, but she rapidly went into severe sepsis with multiple organ failure. The leukemia showed no response to chemotherapy, progressed rapidly, and the patient died.

Conclusions: Malignant hypercalcemia is associated with a poor prognosis in leukemia, and might need a more aggressive therapy.

MeSH Keywords: Child • Hypercalcemia • Precursor Cell Lymphoblastic Leukemia-Lymphoma

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Background

Malignant hypercalcemia is a rare finding in the pediatric population, the overall incidence being at 0.4–1.3% [1]. Most often it is described in solid tumors, such as Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, non-Hodgkin lymphoma, and in rare situations associated to acute leukemia or chronic myeloid leukemia, mostly in the accelerated or blast phases [1–4]. The mechanism is most likely humoral and dependent on the parathormone-related protein (PTHrP) [3,5]. The clinical manifestations vary according to the values of hypercalcemia, and can lead to life-threatening symptoms. Most commonly, patients present with nausea, vomiting, and constipation, but high levels can also present with arrhythmias and renal failure. Early management of hypercalcemia starts with aggressive hydration, forced diuresis with furosemide, and calcitonin respectively [5]. If necessary, therapy with bisphosphonates, such as zoledronic acid, pamidronate, or clodronate, is another option. Dialysis can be instituted if there is no response to medical treatment, or in life-threatening situations [6]. Denosumab, a monoclonal antibody, can be used in refractory disease [3].

We present the case of a 6-year-old female patient diagnosed and treated in our clinic for acute lymphoblastic leukemia with secondary malignant hypercalcemia.

Case Report

Our 6-year-old patient was first diagnosed in August 2016 when she came with malaise, abdominal pain, vomiting, and bloody diarrhea. Clinical examination, peripheral hematological tests, bone marrow aspirate, and immunophenotyping confirmed the diagnosis of B-cell precursor acute lymphoblastic leukemia with paraneoplastic hypercalcemia (Table 1). The initial level of calcium was at 14.9 mg/dL, with signs of tumor lysis syndrome, with high uric acid (9.9 mg/dL) and renal failure (BUN 66 mg/dL and creatinine 1.01 mg/dL). We as well determined the values of PTH and 1,25-OH-vitamin D, which were both decreased.

Intensive chemotherapy was started according to the IC-BFM ALL 2002. Concurrently we administered calcitonin intramuscularly (4 UI/kg every 12 hours), abundant hydration (3.000 mL/m^2) and furosemide starting with 1 mg/kg/day, and then up to 3 mg/kg/day. Calcium levels started to decrease, and the patient went into complete remission after the induction therapy.

After 4 months, during the consolidation therapy, the patient presented again with malaise, vomiting, diarrhea, and high calcium levels. Very early relapse was diagnosed by bone marrow aspirate and immunophenotyping and we started intensive chemotherapy according to the IC-BFM ALL 2002 REZ (Table 1). Calcium levels were high, but this time the patient did not experience tumor lysis syndrome with renal failure (Table 2).

Table 2. Comparative values of parameters at diagnosis and at relapse.

	Diagnosis	Relapse
Total calcium	14.9 mg/dL	15.5 mg/dL
Uric acid	9.9 mg/dL	
BUN	66 mg/dL	29 mg/dL
Creatinine	1.01 mg/dL	0.62 mg/dL
Peripheral blasts	1.600/mm^3	Absent
Bone marrow aspirate	97% blasts	32% blasts
PTH	10.1 pg/mL	Not performed
1,25-OH vitamin D	<5 pg/mL	Not performed

Table 1. Characteristics of leukemia at diagnosis and at relapse.

Leukemia	Diagnosis	Relapse
Leucocytes	12 400/mm^3	4000/mm^3
Bone marrow aspirate	97% blasts with a morphology of acute lymphoblastic leukemia, L1 (FAB classification)	32% blasts with a morphology of acute lymphoblastic leukemia, L1, relapse 1
Immunophenotyping	95% pro-B CALLA positive, with aberrant coexpression of myeloid marker (CD33) and partial maturation asynchronism (partial IgM positive).	95% pro-B CALLA positive, with aberrant coexpression of myeloid marker (CD33, CD13)
Translocations	Negative BCR-ABL, TEL-AML, MLL	negative BCR-ABL, TEL-AML, MLL
Karyotype	10 metaphases had a karyotype of 45,XX,+6,–9,–12, and the rest were with normal karyotype of 46,XX	Not performed

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Table 3. Calcium level variations after zoledronic therapy.

	Day 1 – zoledronic acid administration	Day 2	Day 3 – initiation of calcium supplementation	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Calcium levels (mg/dL)	13.7	12.2	8.6	7.9	7.6	7.3	8.1	8.7	9.2

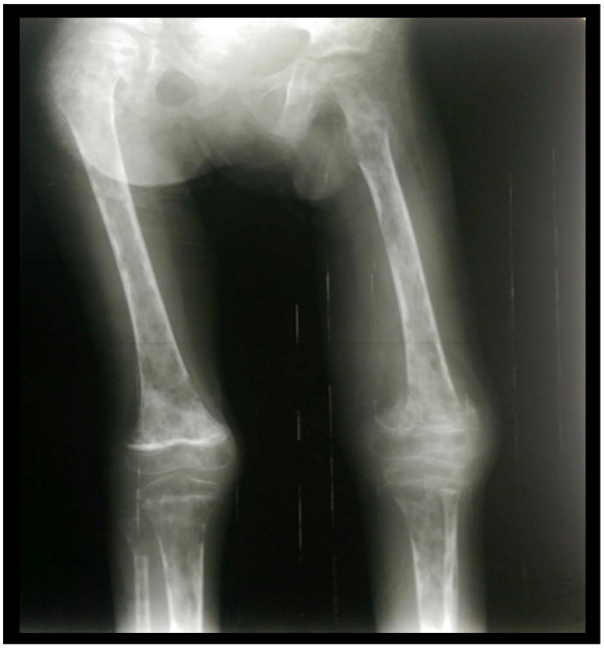

Figure 1. Bone radiography: severe osteopenia. Left distal femur fracture. Left proximal femur callus formation (possible old fracture).

We first controlled hypercalcemia with calcitonin (4 UI/kg every 12 hours), but at the third dose the patient developed blurred vision, so calcitonin had to be stopped. The patient developed, due to severe osteolytic lesions, a spontaneous bone fracture of the left femur, so we found it necessary to start bisphosphonates. The patient received an intravenous dose of 2 mg zoledronic acid, developing thereafter moderate hypocalcemia with the need of calcium supplementation for approximately 10 days (Table 3). After the stabilization of calcium levels, we switched to clodronate orally. Unfortunately, she experienced another bone fracture of the contralateral leg and needed a pelvipedios gypsum immobilization (Figure 1). After 8 weeks of gypsum immobilization association with clodronate, consolidation of bone fractures was achieved.

The patient didn't respond to induction chemotherapy, after the first 2 blocks, we declared progressive disease, so third-line therapy with clofarabine was started.

Due to severe pancytopenia, gypsum, and prolonged immobilization she developed bedsores, which evolved into necrosis. Cultures were collected and infection with *Lichtheimia corymbifera* was diagnosed. We decided to start treatment with posaconazole orally, but unfortunately, the patient developed severe sepsis, with multiple organ failure.

At the same time, her leukemia showed no response to chemotherapy with clofarabine and the patient died with progressive disease.

Discussion

Malignant hypercalcemia is very rare in children, and has been described mostly in solid tumors and lymphomas. The pathogenesis describes a humoral pattern dependent on the PTHrP. There are 3 different known mechanism, from which the humoral pattern is the most common one, where both the PTH and the 1,25-OH vitamin D levels are low and the PTHrP level is high [3]. The other 2 mechanisms, the direct invasion of the bone and the 1,25OH-D mediated one, are characterized by low PTHrP level and low PTH level. The level of 1,25OH-D is only high in the pattern it mediates [3,5–7]. Being unable to determine the level of PTHrP, we only assumed that our case had the humoral pattern, being characterized by both low PTH and 1,25OH-D levels.

Studies have underlined the association of malignant hypercalcemia with a B-precursor phenotype leukemia with aberrant expression of CD13 and CD33, a leucocyte count of less than 20 000/mm^3 at diagnosis, with the hypercalcemia being present as well at the time of diagnosis as at the time of relapse. All these were confirmed in our case, as well [8].

There are some published case reports that link the malignant hypercalcemia to the translocation (17;19) [8–12]. The t(17;19) (q22;p13) translocation generates the E2A-HLF chimeric transcription factor and is associated with a high risk of relapse and poor prognosis, with an event-free survival (EFS) at 5 years of 0% [8,10,11]. This was confirmed also in our case, as the patient had a very early relapse and the leukemia was refractory even to third-line therapy with clofarabine, leading to the death of the patient.

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Treatment of paraneoplastic hypercalcemia depends on the level of calcemia. With only low hypercalcemia protocols recommending the use of calcitonin, diuretics such as furosemide, concomitantly with aggressive hydration. In cases with high levels of calcemia, or a poor response to the first-line treatment, and nonetheless in life-threatening situations, the use of bisphosphonates is recommended. Bisphosphonates are rarely used in children, because of their early and late potential side-effects. However, pamidronate has been shown to be efficient with few side-effects in adults with malignant hypercalcemia [13]. Studies have shown that hypercalcemia decreases faster if bisphosphonates are used [14,15]. Little is known about the correct dosage, but there are some suggestions regarding its administration. Doses range from 0.025 mg/kg to 0.05 mg/kg, and as well-fixed doses of 4 mg of zoledronic acid [3,7,16], and a dose of 1 to 2 mg/kg, with a maximum of 60 mg of pamidronate [2]. We decided to administer only 2 mg of zoledronic acid. Even with a smaller amount, the patient still developed hypocalcemia and needed calcium supplementation for more than 1 week. We did not experience any cardiac side-effects. Even though we continued to administer clodronate orally after the calcium levels stabilized, the patient still suffered another bone fracture.

Another particularity of our case was the infectious complication with *Lichtheimia corimbyfera*, a fungus known to infect immunosuppressed patients. It most commonly affects the central nervous system (CNS), but in some particular situations can also infect traumatized skin [17]. In our case, due to her severe pancytopenia secondary to intensive chemotherapy, and the immobilization with pelvipedios gypsum, the patient developed bedsores underneath the gypsum. We started local and systemic treatment with antibiotic and antifungals ointments, a broad-spectrum antibiotic, and voriconazole, respectively. The evolution of bedsores was poor with the development of necrosis. Literature studies suggest that the best treatment option for this fungus type is amphotericin B, but this product is not available in our country. Therefore, we decided to start oral posaconazole [17,18].

Conclusions

Malignant hypercalcemia may offer, in acute lymphoblastic leukemia in children, a poor prognosis, as was shown in our case report. The limitation of our case report was the lack of possibility to determine the translocation, both due to the absence of a specialized laboratory at the time of diagnosis, and the impossibility to draw enough bone marrow blood at the relapse, because of high fragility of the bone.

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