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CASE REPORT

Case Report: Pulmonary Alveolar Calcification as a Result of Severe Hypercalcemia due to Acute Lymphoblastic Leukemia.

[version 1; peer review: 2 approved]

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Abstract

Severe hypercalcemia is a rare metabolic disorder in pediatric medicine. This report describes a rare case of severe hypercalcemia and its clinical manifestations in a 2-year-old toddler. The radiological findings caused by hypercalcemia and osteolysis were emblematic of the osteolytic lesions. Hypercalcemia led to massive pulmonary alveolar calcification. The hypercalcemia was successfully treated with pamidronate, a bisphosphonate drug class. Further investigation resulted in a diagnosis of acute lymphoblastic leukemia (ALL). The patient is currently on chemotherapy and has a favorable prognosis. Although severe hypercalcemia alone is an unusual finding as the first sign for ALL, this should be considered, not to mention the radiological images resulted from calcium deposits.

Keywords

hypercalcemia, acute lymphoblastic leukemia, pulmonary alveolar calcification, osteolytic lesions, paediatric case report

Open Peer Review

Approval Status

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Severe hypercalcemia is unusual in children and can be either caused by elevated parathyroid hormone (PTH) or a PTH-independent mechanism. Primary hyperparathyroidism, familial hypocalciuric hypercalcemia, familial hyperparathyroidism and secondary hyperparathyroidism are examples of PTH-mediated causes of hypercalcemia. In patients with these conditions, in the early stages of the disease, there is a rise in PTH (or inappropriately normal PTH - not suppressed at the beginning of the hypercalcemia), which can confound the differential diagnosis^{1,2}.

The most common PTH-independent mechanisms for hypercalcemia are related to malignancies¹⁻³, with many different contributing mechanisms. One such mechanism is local metastatic osteolysis (also known as local osteolytic hypercalcemia or malign humoral hypercalcemia (MHH)), which contributes to hypercalcemia through the production of humoral factors by the tumor. This particular mechanism accounts for 80% of the hypercalcemias related to malignancies^{1,2}. Most MHH are due to PTHrP and, less frequently, by the production of Vitamin D (1, 25(OH) 2D3). Tumors that secrete PTHrP can induce an increase in bone resorption and calcium reabsorption from the distal kidney tubule, raising the plasmatic calcium from both mechanisms¹⁻³.

We report a case of alveolar pulmonary calcification after severe hypercalcemia in a 2-year-old toddler with a diagnosis of acute lymphoblastic leukemia (ALL); a rare condition in the pediatric age group. The radiological images of the osteolytic lesions and the alveolar calcification prompt this report, in the hope that they might help to alert clinicians to this unusual condition.

Case report

A 2-year-old Brazilian white male toddler weighing 11.8kg - previously healthy - presented with vomiting after meals, muscular weakness, generalized pain, abdominal cramps, intestinal constipation and inappetence that had begun 25 days prior to his first examination. There was no relevant information about family history.

He was admitted to the pediatric intensive care unit dehydrated, pallid, referring generalized pain, mainly on legs, arms and in abdomen, and was almost unable to walk. At first, the staff thought it could be sepsis or some endocrinological disorder. However, the initial laboratory tests showed heightened ionic calcium levels in the blood (2.95 mmol/L; normal: 1.11 to 1.40 mmol/L). Other laboratory analyses showed hemoglobin: 9.5 g/mL, white blood cell count: 9,460 cells/mm³, platelet count: 206,000/mm³. Urinalysis showed an elevated leukocyte presence (100 leukocytes/field; normal: < 10/field).

As soon as we received the results of the calcium analysis we submitted the patient to a pelvic X-ray to check calcification status. The X-ray revealed substantial osteolysis (Figure 1).

We started treatment for hypercalcemia with hydration and low doses of furosemide (1mg/kg/day divided into 3 doses, duration 2 days) in order to raise the calcium excretion by the kidneys². We decided to start pamidronate (0.5mg/kg/day, duration 3 days) – a second-generation bisphosphonate class drug – to stop the osteolysis by the inhibition of calcium resorption². The symptoms of hypercalcemia subsided and the patient improved.

Figure 1. Pelvis X-ray showing osteolytic lesions secondary to bone resorption (red arrows).

Subsequent laboratory analysis showed that PTH was low at 8 pg/mL (normal: 10 to 65 pg/mL), calcitonin was normal at 8 pg/mL (normal: less than 12 pg/mL) and 1, 25(OH) 2D3 was low at 21 ng/mL (normal: 30 to 60 ng/mL).

A myelogram was performed and was compatible with acute leukemia. The immunophenotype showed the presence of immature T-type cells that expressed intracytoplasmic CD3 antigens, CD7, CD5, CD1a and partial terminal deoxynucleotidyl transferase (TdT). The presence of CD45 at moderately high levels and a lack of CD2 expression in the studied cells were also observed.

The patient underwent chemotherapy based on the standard Berlin-Frankfurt-Munich (BMF) protocol for pediatric ALL. Complete clinical remission occurred after the first cycle of chemotherapy. As a result, calcium levels returned to normal (ionic calcium: 1.2 mmol/L).

Seven months after starting treatment, fever and bacteremia occurred, with no associated neutropenia. An infectious disease screen was performed (blood and urine cultures included), and chest x-ray revealed multiple dense nodular structures. A CT scan confirmed structures resembling calcium nodules not exceeding 1 cm in diameter with peribronchovascular distribution, affecting both lungs mainly in the inferior lobes (Figure 2). Plasma calcium levels (ionized calcium: 1.2 mmol/L) were normal at that time. Tests for fungal infection, and specifically for *Aspergillus spp.*, gave negative results. We also tested for *Cryptococcus neoformans* (agglutination test), *Cytomegalovirus spp.* (antigenemia), tuberculosis (three gastric lavages) and respiratory viruses (nasal secretion tests), with all negative results. The patient had no respiratory symptoms or hypoxemia. Despite the negative results, while the search for an infectious agent was ongoing, he received empiric antibiotic therapy, cefepime (150mg/kg/day) and vancomycin (60mg/kg/day) for 10 days, and liposomal amphotericin B (5mg/kg/day) for 7 days.

The patient was free from infectious or respiratory disorders. Therefore we attributed the nodules observed in the CT images (Figure 2) to previous hypercalcemia which possibly led to a process of pulmonary

Figure 2. Thorax CT scan: pulmonary alveolar calcification.

alveolar calcification. We did not perform a biopsy, since we saw no benefit to the patient of doing so.

Presently the patient is on maintenance chemotherapy with methotrexate (20mg/m²/once a week) and 6-mercaptopurine (50mg/m²/day) completing 106 weeks of treatment.

Discussion

Hypercalcemia in children is rare, especially when it is associated with signs and symptoms that precede a malignant disease. The etiology of hypercalcemia in children is different from adults^{3,4}. Primary hyperparathyroidism and malignant diseases accounts for 90% of hypercalcemia in adults, but both these conditions are rare in children. The first association between hypercalcemia and malignancy was demonstrated by Myers⁵. The incidence of hypercalcemia in pediatric malignant diseases has been reported to be from 0.4% to 1.3%.

Alveolar calcification in itself is a rare condition, often associated with hypercalcemia^{6,7} and has been reported only rarely in literature^{6,7} in association with acute leukemia, making this an unusual finding.

At first, the atypical clinical presentation of this case – the signals and symptoms associated with hypercalcemia - led to a wrong turn

in the diagnostic path, seeming to indicate sepsis or endocrine disorders, before we knew about the calcium status. Thereafter, once the cause of the hypercalcemia was detected, our team of specialists acted in harmony and quickly came to a diagnosis.

The treatment of hypercalcemia depends on the primary cause³. Hydration and bone resorption inhibition with bisphosphonate agents are the most important interventions. Bisphosphonate treatment forms the basis of therapy for malignancy-associated-hypercalcemia, and may provide the necessary time for other antitumor therapies to act. Bisphosphonates (in the same mechanism of action used to treat osteoporosis), prevent the bones from losing calcium in primary hyperparathyroidism, but do not decrease the calcium levels. However, when the hypercalcemia is PTH-mediated, surgery is the standard therapy when possible.

The atypical radiological images, if they had not been associated with severe hypercalcemia could have led to unnecessary procedures like biopsies, or the wasteful use of other therapies, like antibiotics and antifungals.

For the clinician it is important to consider a diagnosis of pulmonary calcium alveolar deposits when faced with images resembling what we present in this report, and when other clinical issues are compatible so that a rapid diagnosis is possible, with the hope of sparing the patient unnecessary therapies.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the parent of the patient.

Author contributions

JCJ prepared the first draft of the manuscript, EB was from the oncologist team, GSSF prepared the images, NAF and WBC contributed with their expertise for the therapeutic plan. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Ana Paula Panzeri Carlotti

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The authors report a rare case of severe symptomatic hypercalcemia as the initial manifestation of acute lymphoblastic leukemia associated with massive pulmonary alveolar calcification which was diagnosed several months later. The case is well documented and image findings are striking. This case report may be useful to alert pediatricians for the diagnosis of malignancy and also favor an early investigation of metastatic calcification of soft tissues in patients with such a severe degree of hypercalcemia.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 02 June 2015

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Jerry Zimmerman

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This article submitted by Colleti and colleagues from Santa Catarina Hospital, São Paulo, Brazil, provides an interesting case report of an unusual entity, namely pulmonary alveolar calcification. The report is well documented and the conclusions not overstated. However, additional data, if

available would be of interest. Specific comments regarding the manuscript are noted below:

1. 'Acute lymphoblastic leukemia', not 'acute lymphoblastic leukemia'.
2. At the time of initial presentation, what was the calcium x phosphate product? If the tumor burden was high and ongoing lysis of leukemia cells was occurring, serum phosphate might also be expected to be elevated and contributing to the calcification of soft tissue.
3. Did the patient present with hypertension?
4. Was a shortened QT interval noted on the admission EKG?
5. Did the medical team specifically inquire about a family history of multiple endocrine neoplasia?
6. At the time of initial presentation, did radiographs demonstrate any evidence of soft tissue calcification? Was calcification of the lungs present on admission; was nephrolithiasis present?
7. The CT scan reproduced in Figure 2, also appears to demonstrate calcification of the heart and great vessels, as well as severe osteopenia of the lower thoracic vertebrae. Did the patient exhibit any structural cardiac problems, such as calcified valve leaflets by echocardiography? Did the patient exhibit any neurological findings attributable to thoracic vertebral osteolysis?
8. Although biphosphonates represent the safest approach to therapy for this patient, is there any role for calcitonin, mithramycin, and indomethacin?
9. It is probably worth mentioning pulmonary alveolar microlithiasis as well as the SLC34A2 gene mutation in the Na/PO₄ co-transporter, as other causes of pulmonary alveolar calcification.
10. Given the appearance of thoracic CT imaging, longitudinal pulmonary function testing is probably warranted for the patient presented.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 21 Jun 2015

Jose Colleti Junior, Santa Catarina Hospital , São Paulo, Brazil

The comments of Dr Zimmerman about this article are relevant and helpful.

I will try to elucidate some questions as follows:

1. The phosphate was really high at the initial presentation, contributing to the calcification of soft tissue;

2. The patient did not have hypertension;
3. The initial EKG was normal (we did not expect that);
4. There was no evidence of family neoplasias;
5. We considered other drugs, besides bisphosphonates, to treat the hypercalcemia. We decided on pamidronate because of the availability, and our personal experience;
6. Although the thoracic CT imaging is striking, the patient did not present any clinical signal of respiratory disorder.
7. The patient is still undergoing treatment and is doing well.

Competing Interests: I have no competing interests to disclose.

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