Atypical Presentation of Acute Lymphoid Leukemia in Child: Case Report

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Apresentação Atípica de Leucemia Linfoide Aguda em Criança: Relato de Caso

Presettación Atípica de Leucemia Linfoide Aguda en Niño: Relato de Caso

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Abstract

Introduction: Acute lymphoblastic leukemia (ALL) is the most common malignant neoplasm in children and the leading cause of cancer death in this age group. Hypercalcemia associated with frank osteolytic lesions is a rare presentation of ALL. **Case Report:** 9-year-old male, 37 kg, presented with headache, pain and functional impotence in the lower right leg for 15 days. Laboratory tests showed elevation of erythrocyte sedimentation rate and C-reactive protein with hypercalcemia. Imaging studies revealed bone demineralization and diffuse osteolytic lesions. Bone marrow aspiration showed 10% of blasts, which did not characterize leukemia. Due to the improvement of his clinical condition, the patient continued the clinical investigation as an outpatient. Biopsy of lytic lesion in the hip and new bone marrow aspirations detected higher number of blasts and confirmed the diagnosis of ALL. Treatment was initiated, following the protocol of the Brazilian Group of Treatment of Leukemia in Childhood, 2009. After two years, he was well and without disease. **Conclusion:** Hypercalcemia is associated with only 0.6% to 4.8% of all ALL cases. The patient presented only diffuse bone pain and hypercalcemia, without the usual symptoms, which makes his clinical condition even rarer, with such presentation being very scarce in the literature. Although uncommon, hypercalcemia and diffuse osteolytic lesions may be the first and only manifestations of ALL in the pediatric range. The present report is important in helping to formulate early diagnosis of childhood leukemia, even in the presence of an atypical clinical condition.

Key words: Precursor Cell Lymphoblastic Leukemia-Lymphoma; Hypercalcemia; Early Diagnosis; Child.

Resumo

Introdução: A leucemia linfoblástica aguda (LLA) é a neoplasia maligna mais comum em crianças e a principal causa de morte por câncer nessa faixa etária. A hipercalcemia associada a lesões osteolíticas francas é uma rara apresentação da LLA. **Relato do Caso:** Paciente de 9 anos, sexo masculino, 37kg, apresentava cefaleia, dor e impotência funcional em membro inferior direito há 15 dias. Exames laboratoriais evidenciaram elevação de velocidade de hemossedimentação e proteína C reativa com hipercalcemia. Nos exames de imagem, apresentava desmineralização óssea e lesões osteolíticas difusas. Aspirado de medula óssea (MO) evidenciou 10% de blastos, o que não caracterizou leucemia. Pela melhora do quadro clínico, o paciente seguiu com investigação diagnóstica ambulatorialmente. Biópsia de lesão lítica em quadril e novo aspirado de MO detectaram maior número de blastos e confirmaram o diagnóstico de LLA. Iniciou tratamento com protocolo do Grupo Brasileiro de Tratamento de Leucemias na Infância, 2009. Após dois anos, estava bem e sem doença. **Conclusão:** A hipercalcemia está associada a apenas 0,6% a 4,8% dos casos de LLA. O paciente em questão apresentava apenas dores ósseas difusas e hipercalcemia, sem a sintomatologia habitual, o que torna seu quadro clínico ainda mais raro, sendo tal apresentação muito escassa na literatura. Apesar de incomuns, hipercalcemia e lesões osteolíticas difusas podem ser as primeiras e únicas manifestações de LLA na faixa pediátrica. O presente relato torna-se importante ao auxiliar a formulação de diagnósticos precoces da leucemia infantil, mesmo na vigência de um quadro clínico atípico.

Palavras-chave: Leucemia-Linfoma Linfoblástico de Células Precursoras; Hipercalcemia; Diagnóstico Precoce; Criança.

Resumen

Introducción: La leucemia linfoblástica aguda (LLA) es la neoplasia maligna más común en los niños y principal causa de muerte por cáncer en ese grupo de edad. La hipercalcemia asociada a lesiones osteolíticas francas es una rara presentación de LLA. **Relato del Caso:** Paciente de 9 años, masculino, 37kg, presentaba cefalea, dolor e impotencia funcional en miembro inferior derecho hace 15 días. Los exámenes de laboratorio evidenciaron elevación de velocidad de sedimentación globular y proteína C reactiva con hipercalcemia. En los exámenes de imagen, presentaba desmineralización ósea y lesiones osteolíticas difusas. Aspirado de médula ósea (MO) evidenció el 10% de blastos, lo que no caracterizó la leucemia. Debido a la mejora del cuadro clínico, el paciente siguió la investigación diagnóstica ambulatoriamente. La biopsia de lesión lítica en cadera y nuevo aspirado de MO detectaron mayor número de blastos y confirmaron el diagnóstico de LLA. Se inició tratamiento con protocolo del Grupo Brasileño de Tratamiento de Leucemias en la Infancia, 2009. **Conclusión:** La hipercalcemia está asociada a sólo 0,6% a 4,8% de los casos de LLA. El paciente en cuestión presentaba sólo dolores óseos difusas e hipercalcemia, sin la sintomatología habitual, lo que hace el cuadro clínico del paciente aún más raro, siendo tal presentación muy escasa en la literatura. A pesar de inusual, hipercalcemia y lesiones osteolíticas difusas pueden ser las primeras y únicas manifestaciones de LLA en niños. El presente relato se vuelve importante al ayudar a la formulación de diagnósticos precoces de la leucemia infantil, incluso en la vigencia de un cuadro clínico atípico.

Palabras clave: Leucemia-Linfoma Linfoblástico de Células Precursoras; Hipercalcemia; Diagnóstico Precoz; Niño.

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INTRODUCTION

Leukemias are a heterogeneous group of neoplasms originated from the neoplastic cells of the hematopoietic system because of the somatic mutation and monoclonal replication of progenitor cells that can be of lymphoid or myeloid lineage. They are characterized by infiltration of the bone marrow (BM), blood and other tissues. Its evolution can lead rapidly to death or progress slower, being divided in acute or chronic forms, respectively[1,2].

The acute lymphoblastic leukemias (ALL) consist of immature cells B or T, called lymphoblasts[1]. Is the type of most common malignant neoplasm in children and the main cause of death by cancer in this age range[3]. The clinical manifestations of lymphoblastic leukemias as anemia, fever and hemorrhages are related to the functional suppression of the BM. The presence of bone pain, generalized lymphadenopathy, splenomegaly and hepatomegaly are common. In the other hand, the elevation of serum calcium, among other rarer symptoms, is worth mentioned[1,2].

Hypercalcemia is a relatively common finding in the malignant neoplasms that affect adults, especially those derived from the hematopoietic system with approximate incidence of 20%[4,5]. However, hypercalcemia associated to malignancy is a rare disorder in children[6]. Hypercalcemia associated to frank osteolytic lesions is a rare complication of ALL and only a few cases were reported with this presentation[7].

Due to the rarity of this clinical presentation, this case report has the objective of describing a case of ALL with unusual symptomatology, but possible to be found, whose recognition is important for the elaboration of the diagnosis in question.

CASE REPORT

Nine years old male patient, 37 kg, from Paranavaí - PR, without relevant personal history, arrived at Hospital Erasto Gaertner (HEG) in Curitiba - PR, on August 2014, complaining of pain and functional impotence of the right lower limb, persistent headache and weight loss of 2 kg (5% of the total weight) in a period of 15 days. In the beginning of the condition, lab tests performed earlier showed the elevation of erythrocyte sedimentation rate and C-reactive protein, with alterations of the blood count. His imaging exams indicated bone demineralization of the hip bone.

In the first evaluation, his general condition was good, bed-ridden, hydrated, pale, eupneic, afebrile and pain in abduction of the right leg. No other alterations were observed.

The lab tests performed at the admission to HEG, an important hypercalcemia was evidenced (Ca total 15.4 mg/dL; value of reference: 8.5 to 11.0 mg/dl). It were initiated measures to reduce the serum calcium associated to diuretic and hydration. The patient was conducted to the ICU in the first day of treatment for continuous monitoring. Because of this condition, new lab and imaging tests were run.

The radiographies and tomographies performed two days after the admission showed that the patient presented bone demineralization with diffuse lytic lesions in the skull, vertebral spine, hip, lower limbs and scapula (Figures 1 and 2). Cervical, thyroid and total abdomen ultrasound were normal.

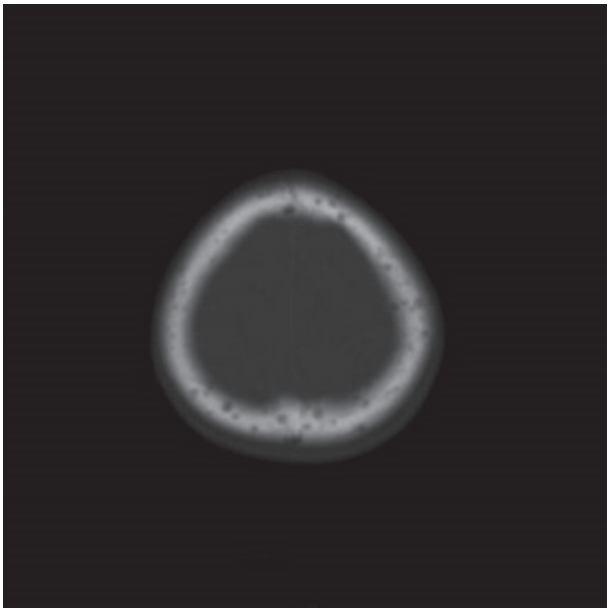

Figure 1. Computed axial tomography evidencing skull osteolytic lesions

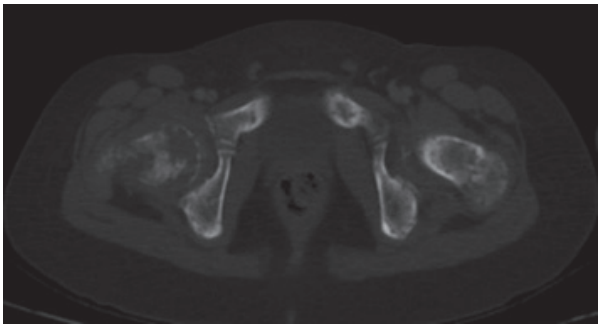

Figure 2. Computed axial tomography evidencing hip osteolytic lesions

Among the diagnostic hypothesis, it were considered hyperparathyroidism (adenoma is the most common case) and leukemia. Serum parathyroid hormone (PTH) dosage

was measured and scintigraphy with technetium 99m SestaMIBI (a radiopharmaceutical that concentrates in the oxyphilic cells of parathyroid, considered hyperfunctional – adenoma or hyperplasia – the focal areas that maintain delayed persistent absorption, approximately two hours after application)[8] both normal, being rejected the hypothesis of hyperparathyroidism in the seventh day of hospitalization. BM aspirate evidenced only 10% of immature cells, which does not characterize leukemia, since it is necessary more than 20% of blasts in marrow for diagnosis confirmation[9].

Because of the good reduction of serum calcium and improvement of the pains, the patient was discharged eight days after the admission with simple analgesia and the diagnostic investigation proceeded in outpatient unit. Lab tests were repeated and new PTH and calcium dosages were normal like the blood count, five days after hospital discharge.

As the diagnosis still remained inconclusive, a biopsy of the hip lytic lesion was performed and new BM aspirate on September 2014, one week after discharge. New anatomopathological exams and immunophenotyping detected the presence of major quantity of blasts in the BM and confirmed the final diagnosis of ALL. Initiated treatment with protocol of the Brazilian Group of Treatment of Leukemias in Childhood (BGTLC-ALL)[10].

The patient evolved gradually and in less than two weeks from the beginning of the treatment, he was painless and walked with support. He had excellent response and after nearly two years from his hospitalization in April 2016, he was well and disease free.

In his last routine visit for revaluation in April 2017, it was identified relapse of the disease isolated in the left testicle. Resumed the chemotherapeutic treatment with new protocol. Currently, he has no new complaints.

The Institutional Review Board (IRB) of Parana League of Cancer Fight approved the study, number CAAE: 91839118.3.0000.0098. The child's legal responsible authorized the publication when they signed the Informed Consent Form.

DISCUSSION

The ALL of type (ALL-B) correspond to approximately 85% of ALL and present signs and symptoms related to the suppression of normal hematopoiesis caused by the accumulation of tumor cells in BM[2]. Therefore, the most commons symptoms of ALL as fatigue, fever, and hemorrhage are related with functional depression of the marrow. Other symptoms as bone pain, generalized lymphadenopathy, splenomegaly, hepatomegaly and testicular dilation are mass effects caused by the neoplastic infiltration. Manifestations of the central nervous system as headache, vomit and nerves paralysis, resulting from the meninges expansion can occur. Among the signs and symptoms that can be encountered, a rare manifestation of ALL is hypercalcemia[2]. The patient of the present report presented only diffuse bone pain and hypercalcemia, without evidences of the most customarily symptomatology.

Hypercalcemia is a finding that can onset in malignant neoplasm in adults in 5% to 20% of the cases, even in the absence of bone metastasis[11]. In the pediatric age range, is a much more common manifestation of malignant neoplasms associated to only 0.4% to 1.3% of the cases[6]. The incidence of hypercalcemia in children with leukemia is around 0.6% to 4.8%[2]. There are several possible mechanisms associated to hypercalcemia, standing out the bone destruction by infiltration of cancer cell, altered osteoclastic activity because of the influence of secreted factors by cancer cells with increased production of vitamin D, PTH or PTH-related protein[2]. A study also suggests that an increase of the levels of certain cytokines as IL-1, IL-6, TNF, PGE2 and TGF-alpha, can be responsible for hypercalcemia in ALL[13]. It is believed that cytokines act as activating factors of osteoclasts, resulting in osteolytic lesions and osteopenia, mainly in the axial skeleton[14]. A study conducted at Hospital St Jude, in the USA identified hypercalcemia in ten of 2,816 children who presented ALL, but in only seven of them, hypercalcemia was present in the beginning of the condition[11]. Another study in Japan identified in a period of 15 years, 25 children in total with ALL associated to hypercalcemia. Nearly 7,500 children were diagnosed with ALL during this period[15]. These articles corroborate the rarity of the symptom manifested by the patient of this case-report.

The therapeutic of hypercalcemia includes hyper-hydration, bisphosphonates and treatment of the baseline disease. In pediatrics, bisphosphonates are still not much utilized because of the relation with osteogenesis[6] adverse events. Initially, however, these were the measures adopted with this patient.

Another uncommon manifestation of ALL is the presence of osteolytic lesions non-associated to neoplastic infiltration. The condition is still more rare when these injuries and hypercalcemia are present in a same patient and this presentation is very rare in the literature[16].

The findings of the cases in discussion – presence of hypercalcemia in children, normal count of lymphocytes, absence of blasts in the peripheral blood, absence of lymphadenopathies, presence of osteolytic lesions and absence of hepatomegaly and splenomegaly were described in only two cases in the world literature[7,17]. However, more than 20 cases were already reported with similar clinical

presentation, that relate the presence of hypercalcemia and ALL in children. Other cases described show the presence of hypercalcemia and osteolytic lesions in pediatric patients, but describe lymphadenopathies[18,13] and hepatosplenomegaly[13] associated. In the Brazilian literature, no other case as the presented in this article was encountered.

There are controversies about the change of diagnosis related with the presence of osteolytic lesions and hypercalcemia in patients with ALL. Some studies suggest that there is no relation between the presence of lesions and worst diagnosis of patients with ALL[9,12,19,20]. Evidences in the literature show that the period of remission of the disease is reduced in patients with osteolytic lesions[11].

CONCLUSION

Despite hypercalcemia and diffuse osteolytic lesions are uncommon findings, they can be the first manifestations of ALL in children. Therefore, the present report becomes important while helping the formulation of early diagnosis of child leukemia, even in the presence of an atypical clinical condition.

CONTRIBUTIONS

The authors contributed equally and substantially in all stages of the work and approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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None.

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