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Case Report

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# *In Situ* Leukemia as Manifestation of Relapse After Allogeneic Transplantation of Bone Marrow of ALL B: A Case Report

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## Abstract

Acute lymphoid leukemia (ALL) is a malignant proliferation of abnormal lymphoid precursors in the bone marrow. It is the most common acute leukemia in childhood, accounting for only 20% of acute leukemia in adults. The clinical presentation is heterogeneous including pallor, fatigue and weakness. Diagnosis is performed through myelogram, bone marrow biopsy and immunophenotyping. Chemotherapy and, in some cases, bone marrow transplantation (BMT) are used to treat the disease. However, the efficacy of treatment in adult patients is still below expected and therapeutic innovations have not increased disease-free survival. In addition, about 20% of patients have relapse, usually generalized, of the disease. This article aims to report the case of a patient previously treated for ALL B presenting localized medullar relapse or *in situ* leukemia.

**Keywords:** Precursor cell lymphoblastic leukemia-lymphoma; Therapeutics; Recurrence

## Introduction

The acute lymphoid leukemia (ALL) is a malignant lymphoproliferative disease with heterogeneous clinical presentation. Immature cells lose the capacity of differentiate and infiltrate the bone narrow leading to a suppression of normal hematopoiesis. It is the most common acute leukemia in children, accounting for only 20% of acute leukemia in adults [1]. The diagnosis is based on bone marrow aspiration, bone marrow biopsy and immunophenotyping by flow cytometry. The symptoms more commonly found are pallor, fatigue and weakness. Nocturnal hyperhidrosis and hemorrhagic manifestations are seen in 33% of the patients [2].

Adults have a poor prognosis. One of the determinants of prognosis is genetics: hyperploidia and t(12; 21) indicate good prognosis, but are characteristic of children and adolescents, being rare in adults. The translocation between the long arms of chromosomes 9 and 22 generating the BCR-ABL gene (the Philadelphia chromosome) implies poor prognosis and are more common in adults. Another important prognostic factor is the minimum residual disease (MRD). It evaluates the response of induction through flow cytometry or other methods. It can be performed at various times of treatment, but the post-induction MRD is the most important prognostic factor [3].

The treatment is based on chemotherapy performed in four stages: induction chemotherapy, consolidation therapy, central nervous system prophylaxis and maintenance [4]. In some cases, hematopoietic stem cell transplantation (HSCT) can be performed. However, treatment of adult patients remains unsatisfactory and therapeutic innovations have not increased disease-free survival rates in the last two decades: adults have a 5-year survival rate of only 30% [3].

## Case Report

A 31-year-old female with history of Pre B ALL treated with hyper-CVAD chemotherapy and allogeneic bone marrow transplantation (BMT) from a compatible related male donor in the first remission. The cytogenetic study was performed at diagnosis, but molecular test for BCR/ABL translocations in blood samples was negative. The transplantation was performed in another institution in a referring center, far away from her home city. It was used a conditioning treatment with busulfan 16 mg/kg, orally, for 4 days and cyclophosphamide 120 mg/kg, IV, for 2 days and prophylaxis of graft versus host disease (GVHD) with cyclosporine and methotrexate for 6 months after HSCT. The cell source was peripheral stem cell. There are scarce data about this period of treatment.

Three years after the transplantation, already in no use of

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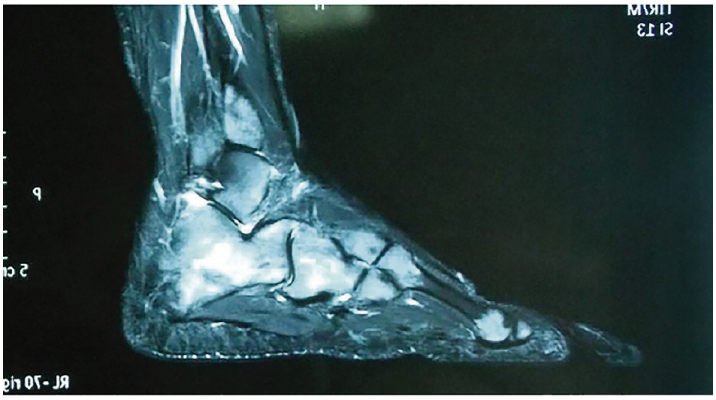

**Figure 1.** Nuclear magnetic resonance imaging of the foot.

immunosuppressors nor showing any sign of GVHD, the patient presented with pain in both feet. The pain was more intense in ankle and it did not improve with analgesics. Due to suspicion of recurrent disease, a bone marrow aspirate with immunophenotyping was performed, but no alterations were detected.

In face of the persistence and progression of the pain, a nuclear magnetic resonance imaging (MRI) of both feet was performed, revealing non-expansive, permeation-like lesions in the bone marrow of various limb bones (Fig. 1). Since there was high probability of relapse of the disease, another bone marrow aspirate in iliac crest with immunophenotyping and a bone marrow biopsy were performed. The results, however, did not indicate activity of the disease. The chimerism analysis showed donor complete chimera. Lactate dehydrogenase (LDH) and cerebrospinal fluid (CSF) were unremarkable.

Due to the persistence of pain and MRI findings, multiple biopsies of the lesions were performed, which were compatible with lymphoblastic non-Hodgkin's lymphoma type B/ALL, with exclusive bone marrow involvement (Fig. 2). The immunohistochemistry study was positive for the following markers: CD19, CD79a, CD10, CD20, CD34 and TdT. These markers were negative: CD3, CD56, CD33 and CD13. No molecular or cytogenetics analysis was done in the material mostly because paucity of these exams in our city.

Because of two bone marrow aspirates with immunophenotyping and an iliac crest biopsy presented with no alterations, the finding was interpreted as localized marrow relapse or "*in situ*" leukemia.

The patient was again referred to a specialized center in another city and received donor lymphocyte infusion (DLI). However, after 4 months of treatment, the patient died due to infections complications. There was not enough information regarding her last treatment.

## Discussion

The results obtained from the treatment of adult patients with ALL are significantly inferior to those observed in children. Only 25% of adult patients achieve a 5-year disease-free survival and long-term survival is obtained in 38% of the patients [5]. Treatment of ALL can be performed with a chemotherapy regimen and HSCT [2].

Although there are studies and meta-analysis comparing chemotherapy and HSCT [6], indications of transplantation in adults in first remission are not accurate and require continuous updating [5]. However, risk stratification and minimal residual studies can be helpful to define the patient who benefits

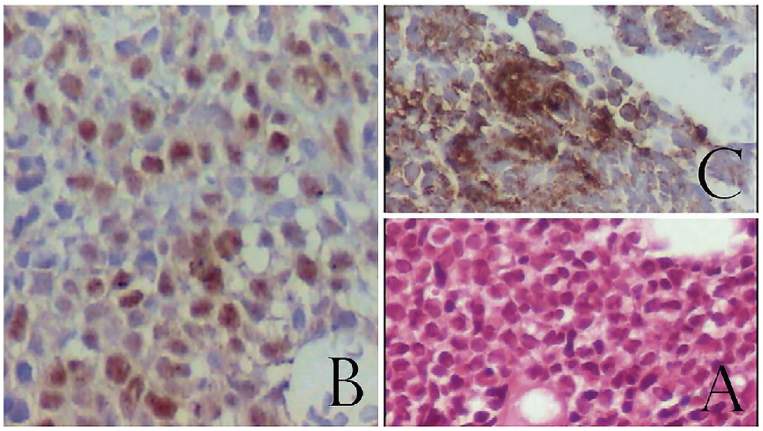


**Figure 2.** Bone marrow biopsy. (A) H&E staining showing infiltration by blast cells. (B) TdT positive cells confirming immature lymphoid cells. (C) CD20 positive cells confirming B cell ontogeny.

most from the transplant.

Allogeneic transplantation has been shown to be effective in adult patients with high-risk ALL. Transplant benefit was reported in young adult patients with severe disease in first remission or patients in second remission. The transplantation from a related compatible donor was the best option [1].

In addition, the importance of this therapy has already been demonstrated in non-severe patients with a living related donor, raising the question if it is the best option for patients in first remission [7]. Those studies do not address the access of the population to all treatments available. In Brazil, the BMT is a good option for patients who do not have entirely access to new drug, clinical trial or even the full diagnostic studies like our patient.

About 20% of the patients present with relapse [8], commonly affecting the bone marrow and, potentially, any tissue in the body, particularly the gonads and the nervous system. In these cases, the bone marrow aspirate is a good tool to detect the relapse. Relapses isolated in other organ except bone marrow are rare, and are called lymphoblastic lymphomas [9]. Our patient did not have hematologic relapse detected with the classical methods.

In the case report, relapse occurred only in the bone marrow of the foot bones. The myelogram and immunophenotyping of the sternum and iliac crest did not present with any alterations, delaying the diagnosis. The disease was only identified by an imaging exam which demonstrated a lesion leading to a biopsy to confirm the diagnosis. Relapse *in situ* as described above is extremely rare. As far as we know, this is the first case reported in the literature with this pattern of "*in situ*" relapse after HSCT. Although the "*in situ*" relapse was seen before systemic disease appears, the outcome was dismal as predict, despite the treatment. Therefore, in patients with ALL and localized bone pain of obscure origin, a normal myelogram should not initially rule out the possibility of relapse.

### Conclusions

ALL in adults is very difficult to cure. BMT is a good option in some cases, but relapses, even in uncommon sites, still remains a challenge. Clinical suspicious and monitoring are, maybe, the best weapons to detect an early relapse that can be treated as soon as possible. Even little symptoms must alert the physician to seek beyond the obvious.

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## Conflict of Interest

None.

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