

Bone marrow necrosis caused by Acute Leukemia: a case report

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Abstract

Bone marrow necrosis (BMN) is an entity resulting from an infarction of the bone marrow stroma without involvement of the cortical bone. It is a serious complication which is associated with malignant neoplasia (among other diseases), with acute leukemia being the most described cause. From these cases, about 18% are acute lymphoblastic leukemia (ALL), affecting less than 0.5% of patients with this pathology. Its histopathology is marked by the depletion of fat cells in an eosinophilic medium with the presence of amorphous material in at least 50% of the sample. The presence of BMNs in acute leukemia suggests a worse prognosis and lower remission rates. This observational study describes a case report of BMN caused by acute leukemia, with the data being obtained from the electronic medical record in the UNIVASF University Hospital System (UH).

Keywords: Lymphoblastic Leukemia; Bone Marrow; Necrosis.

Introduction

Bone marrow necrosis (BMN) is an entity characterized by stromal

infarction of the bone marrow with preservation of the cortical bone. Its incidence is influenced by the type of study conducted (in vivo or post-

mortem) and according to the diagnostic criteria used, ranging from < 0.5% to 37% [1].

Although it is currently recognized as a distinct entity, it frequently occurs as a serious complication from several diseases, among which acute leukemia is the most described cause. From these cases, about 18% are acute lymphoblastic leukemia (ALL), affecting less than 0.5% of patients with this pathology [2, 3].

Its histopathology is marked by the presence of amorphous material and depletion of fat cells under a destroyed and eosinophilic architecture in at least 50% of the sample [1]. The presence of BMN in acute leukemia suggests a worse prognosis and lower remission rates [2]. This is a descriptive case report type study that aims to describe and warn when there is a suspicion of BMN, which is an acute, rare and fatal observation of leukemia.

Case report

A 15-years-old male was admitted in the emergency department with a history of high fever and cervical lymphadenopathy for 20 days. He developed abdominal pain, absence of bowel movements, and weakness in the lower limbs in the last 6 days. The family reports that there was significant weight loss in the period but does not know how much. They denied comorbidities. Complementary exams are shown in table 1. The patient had negative urine and blood cultures.

The first myelogram (Figure 01) revealed apparent hypercellularity with amorphous material and apoptotic cells in all fields, denoting necrotic material. Patient underwent myelogram in both iliac crests to be sure the samples were representatives, and the same findings were observed.

Table 1. Laboratory tests performed in the first week of hospitalization.

Complementary Exams	Day 1 (Admission)	Day 3
Hemoglobin	11.5 g/dL	10.5 g/dL
Hematocrit	31.1%	29.8%
Mean corpuscular volume	81 fL	83 fL
Mean corpuscular hemoglobin concentration	37 g/dL	35 g/dL
Mean corpuscular hemoglobin	29.7 pg	29.2 pg
RDW*	14.6%	15%
White blood cell count	3870/mm ³	3370/mm ³
Segmented Neutrophils	697/mm ³	607/mm ³
Lymphocytes	2245/mm ³	2393/mm ³
Monocytes	270/mm ³	303/mm ³
Band Neutrophils	Zero	67.9/mm ³

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Platelets	27.000/mm ³	22,000/mm ³
Urea	56.1 mg/dL	47.7 mg/dL
Creatinine	1.1 mg/dL	0.8 mg/dL
LDH**	5.831.1/L	2791.5 U/L
HBsAg	Non-reagent	-
HCV rapid test#	Non-reagent	-
24h proteinuria	1082.0 mg	-

Legend: * Red Cell Distribution Width; ** Lactic Dehydrogenase; # Hepatitis C vírus.

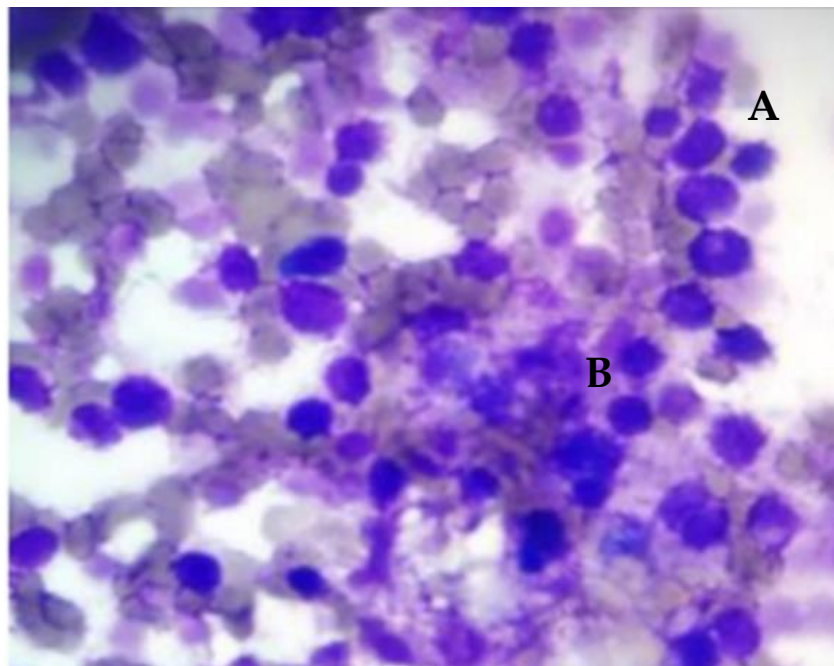


Figure 1. Myelogram showing necrotic material. A- Hematopoietic Cell Outlines (Few Pyknotic Nuclei); B- Bone Marrow Tissues with Coagulative Necrosis

The patient was referred to a Pediatric Oncology Service in the area on the fifth day of hospitalization for further investigation. Bone marrow biopsy confirmed extensive area of necrosis, with no viable marrow in the sample examined.

However, a peripheral blood smear was performed on the ninth day (D9) of hospitalization in the second hospital, which revealed infiltrate of

small-intermediate blasts with some large cells, high nucleus-cytoplasm ratio, no cytoplasmic granulations, intermediate chromatin with poorly evident nucleoli, suggestive of lymphoid blasts. The differential analysis showed leukometry of 43.940 cells/mm³, differential; blasts count of 73%, segmented count of 2% and lymphocytes count of 25%.

The immunophenotyping of the bone marrow sample showed a population of cells of low internal complexity and intermediate CD45, making up 84.2% of the acquired events and presenting positivity for the following main markers: CD10 (partial), CD19, CD22, Cd38 (moderate), CD58, and - cCD79a consolidating the diagnosis of common B-cell Acute Lymphoblastic Leukemia.

Analysis of karyotype of bone marrow with GTG-banding approach (G-bands by Trypsin using Giemsa) showed 46, XY, -17, +mar[3], with a low mitotic index. At t(9:22); t(12:21); t(1:19); t(4:11) were investigated in the bone marrow through the BCR-ABL1, ETV6-RUNX1, TCF3-PBX1, MLL-AFF chimeric products by molecular biology (RT-PCR) and were negative [3].

According to the European Group Berlin-Frankfurt-Münster 2002 (BFM) [4], the patient was classified as intermediate risk, as he was over 6 years old, had an initial leukocyte count above 20,000 and had bone marrow in remission on day 33 of treatment.

Although bone marrow assessments on day 15 showed persistence of necrotic material, but at this point the patient was doing well, with regression of symptoms and bone marrow was recovered in subsequent evaluations. The patient is still in the consolidation phase, (around 6 weeks of treatment), with post-induction

myelogram showing complete hematologic response.

Discussion and Conclusion

BMN pathophysiology involves factors such as microvascular insufficiency and hypercellularity which invariably culminates in spinal cord infarction when added to an environment full of proinflammatory cytokines. According to some authors, it can be classified in degrees according to the extent of the necrosis area: grade I corresponds to light necrosis when focal, with extension <20%; grade II corresponds to moderate necrosis when it covers an area between 20-50% of the sample; grade III represents extensive necrosis, in which > 50% of the bone marrow area is affected [2, 5].

It is frequently observed in the context of hematologic malignancies, as recorded in a series of 240 cases, in which ALL was the main disease associated with bone marrow necrosis (18% of cases). The most common clinical manifestations of patients with BMN associated with ALL are bone pain and fever, present in 90% and 75% of the cases, respectively [6].

In our described case, the patient presented fever as one of the initial manifestations of his condition, but, unlike this symptom, bone pain is not usually present at the beginning of the disease, appearing as a symptom in only 22% of cases [6, 8].

Among the laboratory findings, the most common abnormalities are anemia and leukopenia, present in 90% and 68% of the cases, respectively, both present in the described case. However, even though thrombocytopenia is present in only 20% of patients with BMN at levels below 100,000/mm³, this finding is seen in more than 70% of patients with ALL, which suggests the association of the two entities. Lactic dehydrogenase is virtually increased in 100% of BMN cases, and is also altered in ALL, which denotes an extensive necrosis area associated with a disease of high cellular turnover. Such a finding should be valued and favor the suspicion of both diagnoses [6,7,9]. However, the degree of abnormality in exams such as LDH, ferritin and D-dimer did not reflect the severity of the disease or the prognosis in a series of 23 cases of BMN [10].

The prognosis of BMN mainly depends on the underlying disease and the patient's age. A complete response to treatment is significantly lower in patients with ALL associated with bone marrow necrosis than in those who do not have BMN (70% vs 90%, $p = 0.01$) [6]. However, despite the dramatic nature of the clinical features there is enough evidence in the current literature to fit these patients into the High-Risk group and does not necessarily end up with a worse prognosis when associated with ALL.

High cure rates are still observed in these situations [6].

Similarly, there is no clear evidence of etiological factors described for this scenario. However, some retrospective studies in multivariate analyzes have associated chromosome 17 abnormalities with worse overall survival and event-free survival in ALL, especially in older patients, and it is not yet possible to determine the actual prognosis and correlation of this chromosomal alteration with BMN [11].

BMN is commonly associated with fatal outcomes. Although unusual, its association with ALL is well described and associated with lower rates of complete response to treatment. This report reinforces the importance of knowing this relationship and incessantly seeking its diagnosis with the aim of an early therapeutic approach, in addition to demonstrating the best prognosis of the pediatric patient.

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