

Acute lymphoblastic leukemia of childhood presenting as aplastic anemia: report of two cases

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Acute lymphoblastic leukemia is the most common malignancy in pediatric patients; its diagnosis is usually easy to establish as malignant lymphoblasts invade the bone marrow and peripheral blood. Some acute lymphoblastic leukemia patients may initially present with pancytopenia and a hypoplastic bone marrow leading to the initial diagnosis of aplastic anemia. In most of these patients clinical improvement occurs, with normalization of the complete blood count within six months, although recovery can also develop a few weeks after initiating steroid therapy. The etiologic relationship between the aplastic anemia features and the subsequent overt development of acute lymphoblastic leukemia has not been established. We describe the cases of two children who presented with severe infection and signs and symptoms of aplastic anemia confirmed by bone marrow aspirate and bone marrow biopsy that developed acute lymphoblastic leukemia thereafter. No specific therapy for aplastic anemia was administered, nevertheless a full spontaneous recovery was observed in both cases. Acute lymphoblastic leukemia was successfully treated with standard chemotherapy, both children remaining in complete remission 16 and 17 months after their initial aplastic anemia diagnosis.

Keywords: Acute lymphoblastic leukemia; Aplastic anemia; Pediatrics

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in pediatric patients; malignant white blood cells continuously multiply leading to an excess of lymphoblasts in the peripheral blood and the bone marrow.⁽¹⁾ In most children the symptoms arise as a result of the deviation from the normal hematopoietic processes into the production of immature leukocytes, leading to bicytopenia accompanied by leukocytosis. Some patients may initially present with pancytopenia and a hypoplastic bone marrow suggesting the diagnosis of aplastic anemia (AA).⁽²⁾ This aplasia is transient and occurs in about 2% of pediatric ALL cases and is thus considered a preleukemic condition.⁽³⁾ In most of these children an apparent clinical improvement occurs with recovery of the cell count within six months after the initial diagnosis of AA or suddenly a few weeks after initiating steroid therapy.⁽¹⁾

The etiologic relationship between the AA features and the subsequent overt manifestations of ALL is not well established and it remains unclear whether the leukemic process follows the aplasia or if it is already present at the diagnosis of AA. The precise initial event leading to ALL remains unidentified, some studies show data supporting the idea that ALL develops by the acquisition of chromosomal abnormalities, mostly during fetal hematopoiesis, resulting in a subclinical preleukemic clone, and/or postnatal secondary genetic changes.⁽⁴⁾ The need remains to elucidate the circumstances under which preleukemic clones might evolve to an overt ALL, considering the possibility that these clones acting as a pool for leukemic relapses.

Clinical cases

Case 1

A five-year-old male without relevant preexisting clinical conditions presented with perianal pain and fever of 5 days of evolution. At physical examination general pallor and a perianal abscess were noted. Initial complete blood count (CBC) included hemoglobin (Hb) of 5.0 g/dL, leukocytes of $0.209 \times 10^9/L$, neutrophils of $0.006 \times 10^9/L$, and a platelet count of $4.9 \times 10^9/L$ (Table 1). A bone marrow biopsy (BMB) and bone marrow aspirate

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Table 1 - The complete blood counts of Cases 1 and 2 at the time of their first visit at the diagnosis of AA, at discharge after a sudden recovery of hematological values and at relapse, when the diagnosis of ALL was established

Parameter	Diagnosis of AA	Recovery	Diagnosis of ALL
		Case 1	
Time (weeks)	0	3	15
Hemoglobin (g/dL)	5.0	10.0	15.3
Leukocytes (x 10 ⁹ /L)	0.209	5.0	83.07
Peripheral blood blasts (%)	0	0	80
Neutrophils (x 10 ⁹ /L)	0.006	2.0	37.85
Platelets (x 10 ⁹ /L)	4.9	170.0	121.0
		Case 2	
Time (weeks)	0	2	18
Hemoglobin (g/dL)	1.7	11.0	4.6
Leukocytes (x 10 ⁹ /L)	1.18	5.04	28.3
Peripheral blood blasts (%)	0	0	70
Neutrophils (x 10 ⁹ /L)	0.546	1.93	0.146
Platelets (x 10 ⁹ /L)	8.0	110.0	8.6

(BMA) were performed finding a severely hypoplastic bone marrow without the presence of malignant cells. The patient was diagnosed with AA and his infection was treated with 20 mg/kg/day of meropenem (t.i.d.) and vancomycin at 60 mg/kg/day (q.i.d.) for 10 days; he was transfused with two red blood cell (RBC) units and six platelet concentrate units. The patient did not receive steroids initially due to his infection and a pending pathology report; *Escherichia coli* was finally isolated from the abscess culture. Seven days after starting treatment the CBC values showed marked improvement reaching clinical recovery three weeks after the initial diagnosis without further need of steroid therapy. The patient was discharged and followed-up with no further treatment needed. Three months after full recovery, sudden worsening of his general condition developed and a CBC showing Hb of 15.3 g/dL, leukocytes of 83.07 x 10⁹/L with 80% of peripheral blasts, neutrophils of 37.85 x 10⁹/L and a platelet count of 121.0 x 10⁹/L. The immunophenotype corresponded to a B cell population. Standard therapy for ALL was started; the induction regimen included prednisone 60 mg/m²/day divided (t.i.d - days 1-29), vincristine 1.5 mg/m² IV (days 8, 15, 22, 29), L-asparaginase 6000 U/m² IM 3 times/week (M,W,F) for nine total doses (starting day 8), cytarabine 75 mg/m² IV/SQ (days 29-32 and 36-39), intratecal (IT) methotrexate 12 mg (days 1, 8, 29) and adriamycin 25 mg/m² IV (days 1, 8, 15 - used only for the delayed induction regimen for ALL children). The consolidation scheme included vincristine 1.5 mg/m² IV (day 1), 6-mercaptopurine 75 mg/m²/day (days 1-28), and methotrexate 50 mg/m² IV (days 1, 8, 15, and 22). The patient achieved complete remission (CR) without major complications and remains on maintenance with dexamethasone 6 mg/m²/day divided (b.i.d. - days 1-5, 29-33, 57-61), vincristine 1.5 mg/m² IV (days 1, 29, 57), 6-mercaptopurine 75 mg/m²/day (days 1-84), and

methotrexate 20 mg/m² p.o. weekly (starting day 1). After one year of follow up his current CBC consists of Hb 14.1 g/dL, leukocytes 6.85 x 10⁹/L with BMA negative for the presence of blasts, neutrophils 3.67 x 10⁹/L and platelets 241.0 x 10⁹/L. (Table 1).

Case 2

A two-year-old male presented with a 2-week history of upper respiratory tract infection, dark stools, fever, and severe anemic syndrome. In the physical examination hepatomegaly 2 cm below the costal margin was present with no splenomegaly; signs of heart failure, including edema, fatigue, dyspnea, jugular vein engorgement, and heart gallop were identified. The initial radiographic evaluation showed cardiomegaly and the echocardiogram revealed a dilated cardiomyopathy with an ejection fraction of 44%; a correlation with a previous viral infection was suspected and treatment with digoxin was started with excellent response. The CBC showed an Hb concentration of 1.7 g/dL, leukocytes of 1.18 x 10⁹/L, neutrophils 0.546 x 10⁹/L and a platelet count of 8 x 10⁹/L (Table 1). The BMA and BMB showed a severely hypoplastic bone marrow leading to the diagnosis of AA; no malignant cells were present. The patient received 15 mg/kg/day of amikacin (q.i.d.), 100 mg/kg/day of ceftazidim (t.i.d.), for ten days, and transfusion of two packed RBC units and four platelet concentrate units. No steroids were used because the septic condition and pending pathology report. The blood culture was positive for *Escherichia coli*; gradual clinical recovery was seen without additional treatment needed and the patient was discharged ten days after admission with notable improvement in the CBC (Table 1), heart failure signs and decrement of the hepatomegaly to 1 cm below the costal margin; he was followed-up without requiring further therapy. Four months later he was readmitted after ten days of evolution with fever, asthenia, hyporexia, petechiae and presence of multiple adenomegalies, hepatomegaly 3 cm below the right costal margin and grade III splenomegaly. The CBC showed a Hb of 4.7 g/dL, leukocytes of 28.30 x 10⁹/L with 70% of peripheral blasts noted in the BMA, neutrophils of 0.146 x 10⁹/L and a platelet count of 8.6 x 10⁹/L. The patient was treated with the same ALL therapeutic scheme used in case 1 achieving a CR; currently on the maintenance phase ten months after the initial AA diagnosis with the last CBC showing a Hb of 11.9 g/dL, leukocytes 9.12 x 10⁹/L with no blasts present in peripheral blood, neutrophils 6.05 x 10⁹/L and a platelet count of 209.4 x 10⁹/L. His cardiomyopathy has improved gradually and is currently being treated with digoxin.

Discussion

Approximately 40 cases of ALL initially presenting as AA have been reported worldwide. A higher incidence was

noted for women and younger children (< 10 years); in the largest publication available involving 22 patients, ALL appeared after the sudden recuperation of the CBC, with 95% of cases progressing to ALL within six months of initial diagnosis.⁽⁵⁾ A common factor between our two cases and previous studies was the antecedent of a viral or bacterial infection prior to the AA presentation. Reports of ALL remission associated to an infection have been published, although the mechanism has not been established.⁽⁶⁾ Possible explanations include a clonal disruption with a real preleukemic status, coexistence of a severe bacterial or viral infection, increased levels of endogenous corticosteroids that temporarily halt lymphoblastic proliferation and exposure to exogenous toxins.⁽⁷⁾

Flow cytometry studies for both our patients reported a B cell population at the time of ALL diagnosis. One publication has reported a similar case in an adult where the molecular detection of monoclonality in the BMA was made for both the period of AA and at diagnosis of ALL.⁽⁸⁾ Cytogenetic studies may not be useful because at this early stage there is insufficient mitosis and abnormalities may result without being clinically relevant to the later history of the AA. Nevertheless, studies of molecular rearrangements for immunoglobulins or T cell receptors are very sensitive in the detection of a leukemic clone at a stage when ALL cannot be diagnosed by other methods.⁽⁹⁾ A retrospective study detected the presence of the ETV6-RUNX1 fusion in the BMA during the aplastic phase, identifying the leukemic genotype on the aplasia preceding clinical ALL and suggesting that multiple secondary genetic abnormalities can contribute to a dominant subclone several months before a diagnosis of ALL.⁽⁴⁾ The detection of this fusion would require a directed search during the aplastic stage preceding the symptoms of ALL to identify the leukemic clone allowing the subsequent opportune treatment in the preleukemic stage for this form of ALL presentation.

In most of these previous reports, steroid therapy was administered thus probably leading to a partial remission of ALL.⁽⁵⁾ In our two patients, therapy was directed only to the infectious episode, with simultaneous administration of blood products, no anabolic steroids were given and no specific

treatment for the AA was administered; clinical and hematological improvement occurred. This leads us to hypothesize that spontaneous recovery of the aplastic bone marrow could be part of the natural history of this form of ALL presentation. The hypoplastic bone marrow may be a result of an immunological reaction triggered by the presence of leukemic cells to control the leukemic clone proliferation; these cells may produce lymphokines that attack normal hematopoietic cells.⁽⁹⁾ These mechanisms could play a role in explaining the spontaneous recovery of pancytopenia in patients who later develop full blown ALL.

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