A strategy for the clinical remission of acute lymphoblastic leukemia elicited by treatment of β-thalassemia major: A case report

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Abstract. Acute lymphoblastic leukemia (ALL) has been suggested as a long-term complication in patients with β-thalassemia major (β-TM). A 12-months-old male patient was diagnosed with β-TM. The patient required a blood transfusion weekly for 2 years. At the age of 4 years, a splenectomy was performed due to massive splenomegaly and frequent transfusion requirements. The histopathological analysis of the spleen revealed extensive hemosiderosis. ALL-L1 with the T immunophenotype and without central nervous system (CNS) involvement was diagnosed when the patient was 5 years old, and treated with anti-leukemic combination chemotherapy and CNS radiotherapy. The patient completed 24 months of treatment and has been in complete remission for 7 years, without long-term adverse events.

Introduction

β-thalassemia comprises a group of hereditary hematological disorders characterized by abnormalities in the synthesis of the β chains of hemoglobin, resulting in variable phenotypes, ranging from severe anemia to clinically asymptomatic individuals. Patients with β-thalassemia major (β-TM) usually present with severe anemia within the first 2 years of life, requiring regular red blood cell (RBC) transfusions (1). However, transfused patients may develop complications associated with iron overload. Chelation therapy increases patient survival; however, long-term complications include cancer development (2). β-TM is rare among Mexican pediatric patients (3). By contrast, acute lymphoblastic leukemia (ALL) is the most common type of cancer in Mexican children (4,5). Several genetic factors are associated with increased risk of ALL, but the majority of the patients have no identified inherited factors (6,7). Previous studies suggested that ALL may develop as a long-term complication of β-TM treatment (8-10), although the association between these two hematological diseases has not been fully elucidated. We herein describe a case of remission of T-cell ALL in a Mexican male patient with β-TM and analyze clinical data and the association between these two pathologies.

Case report

A 9-month-old male infant, with no known European ancestry, presented in August 2003 to the community hospital with anemia and jaundice. The patient received iron and folic acid supplementation, without improvement of the symptoms. At the age of 1 year, the patient received an RBC transfusion and was referred to a third-level pediatric hospital located in Mexico City due to increased abdominal girth. Upon physical examination, the patient was found to have cervical lymphadenopathy, splenomegaly extending to the lower left quadrant, and hepatomegaly crossing the umbilicus.

The patient's initial complete blood count (CBC) was as follows: Hemoglobin (Hb) 7.9 g/dl, hematocrit 25.8%, mean corpuscular volume 88.6 fl, mean corpuscular hemoglobin 27.1 pg, mean corpuscular hemoglobin concentration 30.6%, and platelet count 91,000/mm^3. The patient's blood type was O positive. The reticulocyte count was 23%, the fetal Hb was 2.58% and HbA2 was 8.87%. The bone marrow aspirate exhibited increased cellularity with normal megakaryocytes, promyelocytes (2%), myelocytes (18%), juveniles (9%), bands (13%), segments (6%), eosinophils (5%), monocytes (0.5%),

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Abbreviations: β-TM, β-thalassemia major; RBC, red blood cell; ALL, acute lymphoblastic leukemia; CBC, complete blood count; CNS, central nervous system

Key words: acute lymphoblastic leukemia, child, Mexican, β-thalassemia major, iron overload

Table I. Comparison between reported cases of ALL in β-TM patients.

	Patients (Refs.)				
	No. 1 (1)	No. 2 (2)	No. 3 (2)	No. 4 (3)	Present case
Sex/age, years	M/8	F/9	M/3.5	M/9	M/5
Nationality	Greek	Iranian	Iranian	Egyptian	Mexican
ALL immunophenotype	-	B-cell	B-cell	B-cell	T-cell
Maintenance treatment of β-TM	Blood transfusion	Blood transfusion	Blood transfusion	Blood transfusion	Folic acid, blood transfusion
Chelation therapy	-	DFO	None	DFO, DFX	DFO
Hydroxyurea therapy	-	-	-	No	No
Age at β-TM diagnosis	4 years	6 months	3 years	12 months	12 months
Treatment	Chemotherapy, cranial radiotherapy	-	-	Chemotherapy	Chemotherapy, CNS radiotherapy
Prognosis	CR, 7 months' follow-up	-	-	CR, MP	7 years in complete remission

ALL, acute lymphoblastic leukemia; β-TM, β-thalassemia major; CR, complete remission; DFO, deferoxamine; DFX, deferasirox; CNS, central nervous system; MP, maintenance phase.

lymphocytes (43.5%) and plasma cells (2.5%); based on these findings, β-TM was diagnosed. Treatment was started with folic acid, ascorbic acid and transfusion therapy. RBC transfusions (10-15 ml/kg/week) were required for 2 years. The iron profile was as follows: Iron, 70 μg/dl; iron-binding capacity, 192 μg/dl; free iron, 122 μg/dl; saturation, 36.4% and ferritin, 1,900 mg/ml. Six months later, chelation with deferoxamine was started at a dose of 40 mg/kg. At the age of 4 years, splenectomy was performed due to massive splenomegaly and frequent transfusion requirements. The resected spleen weighed 1,000 g and histopathological analysis revealed extensive hemosiderosis. One month later, the patient presented with diarrhea and meningitis treated with cefotaxime and vancomycin for 14 days. During the meningitis episode, the patient developed seizures and was treated with phenytoin (6.2 mg/kg/day) for 2 years.

At the age of 5 years and 8 months, the patient presented with infiltrative syndrome and hepatomegaly. CBC showed the following results: Hb, 12.8 g/dl; leukocytes, 90,500/mm^3; and platelets, 263,000/mm^3. ALL-L1 with a T immunophenotype and without CNS involvement was diagnosed. The patient then developed tumor lysis syndrome (TLS) manifesting with nausea, vomiting, hyperuricemia and hyperphosphatemia. TLS was treated with intravenous liquids (3,000 ml/m^2), alkalization (bicarbonate 50 mEq/l) and alopurinol (300 mg/m^2). Dexamethasone therapy (6 mg/m^2/day) was initiated, and the patient responded well. Remission induction was started with vincristine, L-asparaginase, daunorubicin, dexamethasone, and triple intrathecal chemotherapy. The patient developed pancreatitis and septic shock (*Escherichia coli*) after the second dose of L-asparaginase. The patient was treated according to St. Jude Children's Research Hospital protocol for high-risk ALL. In addition, prophylactic cranial radiotherapy (18 Gy) due to hyperleukocytosis of cells with the T immunophenotype (78,000/mm^3). The patient completed 24 months of treatment and chemotherapy has been electively discontinued, without long-term adverse events. The patient's age at present is 16 years and has been in complete remission for 7 years (last follow-up, August 2017). The patient and his parents consented to the publication of the clinical case details.

Discussion

To date, there have only been reports of pediatric cases with β-TM who developed ALL with the B immunophenotype (Table I). To the best of our knowledge, this is the first report of ALL with the T immunophenotype in a child previously diagnosed with β-TM. In the previous cases, the majority of the patients were male. Similarly, other reports indicated that boys with thalassemia are more likely to develop hematological malignancies compared with girls (11,12). In all the cases, the emergence of ALL occurred within 6 months to 8 years after β-TM treatment was initiated. Collectively, these observations suggest that a side effect of β-TM treatment is ALL occurrence, which adversely affects the patient's prognosis. Iron overload resulting from prolonged transfusions has been considered to be carcinogenic, as it has the ability to damage biomolecules, leading to the production of hydroxyl radicals and other reactive oxygen species that induce a wide array of DNA lesions, from base modifications to strand breaks and adducts (13). Additionally, iron accumulation has been shown to induce DNA hypermethylation. The AIEOP group reported that β-TM is the most common genetic disease in ALL patients, excluding Down's syndrome (14). Furthermore, the children of women who received iron supplementation pregnant were more likely to develop ALL [odds ratio (OR)=1.36, 95% confidence interval (CI):1.14-1.63] compared with the children of mothers who were not prescribed iron supplements (15). In this respect, it has been hypothesized that childhood ALL is frequently initiated by a chromosomal translocation event *in utero*, and iron may provide a proliferative advantage to leukemic cells,

thus driving disease progression (16). This suggests that children with β-TM developing ALL may be born with mutations, and iron contributes to the development of leukemia. In addition, Kennedy *et al* demonstrated that genetic variants of the transferrin receptor gene (*TRFC*, rs733655; OR=2.6, 95% CI: 1.44-4.70) are associated with ALL in non-Hispanic white males, further supporting the hypothesis that iron excess mediated by genetic variants increases the risk of childhood ALL (17). However, the majority of patients with β-TM and ALL received chelation therapy. Moreover, Quattrin *et al* reported a similar incidence in leukemia between thalassemia patients and the general population (18). Furthermore, β-thalassemia patients not requiring RBC transfusions also develop hematological malignancies, including ALL, indicating that the simultaneous occurrence of these diseases may be coincidental (12,19).

Of note, evidence indicates an association between T-cell ALL and preexisting ataxia-telangiectasia (AT), reflecting a non-random mechanism of leukemogenesis (14,20). In this regard, *ATM* gene truncating mutations were 12.9 times more frequent in childhood T-cell ALL compared with the normal population (P=0.004) (21). Patients with these pathologies have a poor prognosis. The patient in the present case did not have AT. This report adds to the evidence suggesting an association between β-TM and ALL.

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