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CASE REPORT

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Editor-in-Chief of *World Journal of Clinical Pediatrics*, Dr. Sergi obtained his MD degree with honors (1989) and Pediatric specialization (1993) at the University of Genoa, Italy, and Pathology specialization at the University of Heidelberg, Germany (2001). Dr. Sergi is currently a Full Professor of Pathology and Adjunct Professor of Pediatrics at the University of Alberta, Canada. Dr. Sergi also serves as a Consultant of Carcinogenesis in Experimental Animals at the World Health Organization/International Agency for Research on Cancer (WHO/IARC, Lyon, France) and an "ad-hoc" Peer-Referee for the National Toxicology Program of the National Institutes of Health (Research Triangle Park, NC, United States). His areas of interest are Biology and Pathology of the Cardiovascular/Gastrointestinal System with Gut/Bile Microbiome involvement as well as Bone Cell Biology. Dr. Sergi has authored over 250 peer-reviewed publications indexed in the PubMed literature database (H-index: 23, RG-score: 44.26, > 2500 citations). (L-Editor: Filipodia)

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CASE REPORT

Acute lymphoblastic leukemia in a β-thalassemia intermedia child: A case report

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Abstract

BACKGROUND

β-thalassemia intermedia (βTI) is one of the hemoglobinopathies. It constitutes 10% of β-thalassemia cases and is associated with better quality of life than β-thalassemia major (βTM).

CASE SUMMARY

We recently reported the first case of acute lymphoblastic leukemia (ALL) from Egypt in a child with βTM, and we herein report the first case of ALL from Egypt in a child with βTI. In this report, literature was reviewed for cases of malignancies associated with βTI and the possible factors underling the relationship between the two entities.

CONCLUSIO

We stress that physicians should have a high index of suspicion of malignancies in thalassemia patients if they present with any suggestive symptoms or signs.

Key Words: Acute lymphoblastic leukemia; Thalassemia intermedia; Children; Malignancies; Iron overload; Hydroxyurea; Case report

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Core Tip: Cases of malignancies in patients of β-thalassemia major have been reported. However, rare cases have been reported for malignancies in patients of β-thalassemia-intermedia as it is a non-transfusion dependent anemia. Physicians should have high index of suspicion to diagnose malignancies in patients with β-thalassemia-intermedia.

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INTRODUCTION

Thalassemia represents the most common single-gene disorder worldwide. The total annual incidence of symptomatic individuals with β-thalassemia is estimated at 1 in 100000 throughout the world, of whom nearly 10% have β-thalassemia intermedia (βTI), which is intermediate in severity between the milder thalassemia-minor and the more severe transfusion-dependent β-thalassemia-major (βTM)[1].

We herein report the first case from Egypt with βTI who developed acute lymphoblastic leukemia (ALL).

CASE PRESENTATION

Chief complaints

The reported patient is a 15-year-old girl with βTI, who presented at the age of 3 years with pallor, decreased growth rate and decreased activity. She had severe microcytic, hypochromic anemia with hemoglobin (Hb) of 7.3 g/dL.

History of present illness

Pediatric hematologist workup confirmed the diagnosis of βTI. Her Hb electrophoresis showed 69.9% HbA, 27.2% HbF and 2.9% HbA2. Genetic molecular testing revealed compound heterozygosity for cd-27 (G>T) and cd-39 (C>T) mutations. Hydroxyurea at a dose of 15 mg/kg per day was started, in addition to folic acid.

She was then followed at the pediatric hematology unit at regular intervals to monitor her tolerance to drug therapy, with special attention to hematological toxicity. There were no significant side effects during 7 years of therapy, and the patient showed good response with occasional need for blood transfusions. She underwent splenectomy during her late teens.

History of past illness

At the age of 15 years, she developed generalized bone aches, abdominal pain, persistent fever and dyspnea, and she was referred to our hospital.

Physical examination

On physical examination, there was severe pallor, tachypnea, tachycardia and hepatomegaly.

Laboratory examinations

Initial complete blood picture showed a Hb level of 3.9 g/dL, white blood cell count of 250×10^9/L and platelet count of 640×10^{-9}/L.

Serum electrolytes, cerebrospinal fluid analysis and kidney and liver function tests were normal, except for mild elevation of total serum bilirubin, which was 1.3 mg/dL.

Serum ferritin was 877 ng/dL. Serological studies including Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, hepatitis C virus and hepatitis B virus were negative. Lactate dehydrogenase was 974 U/L, and serum uric acid was 5.6 mg/dL.

Imaging examinations

Her chest X-ray was normal. Abdominal ultrasonography revealed hepatomegaly with calcular cholecystitis and bilateral diffuse renal enlargement. Echocardiography showed mitral valve prolapse with trivial mitral regurgitation.

MULTIDISCIPLINARY EXPERT CONSULTATION

The pediatric hematologist/oncologist assessment requested bone marrow biopsy, which was carried by the hematopathologist

Bone marrow examination revealed 80% blast cells in a hyper-cellular marrow with depressed erythropoiesis and granulopoiesis and normal thrombopoiesis. Immunophenotyping showed lymphoblasts that were CD10 positive, CD19 positive, CD34 positive, TDT positive, HLA-DR positive, CD13 positive and CD33 positive.

Cytogenetic examination showed a normal karyotype with a deoxyribonucleic acid (DNA) index of 1 and negative t(12,21), t(1,19), BCR-ABL and 11q23 translocations/mutations.

FINAL DIAGNOSIS

A final diagnosis of B-acute lymphoblastic leukemia (ALL) with aberrant expression of CD13 and CD33 was achieved.

TREATMENT

Induction chemotherapy of the total XV protocol with prednisone, vincristine, L-asparaginase, doxorubicin, cyclophosamide, cytarabine, 6-mercaptopurine and intrathecal chemotherapy was commenced.

She received multiple packed red cell transfusions, which eventually led to elevation of serum ferritin to 1420 ng/dL. She was then started on oral chelation therapy with deferasirox with no complications.

The patient eventually went into complete remission. She then received consolidation chemotherapy of standard risk of the total XV protocol with four times of high dose methotrexate, 6-mercaptopurine and intrathecal chemotherapy.

She received multiple packed red blood cell transfusions and other supportive measures during the periods of induction and consolidation. The transfusions therapy was given according to the guidelines of pediatric oncologists. They usually transfuse if Hb level is less than 8 g/dL and if associated with pulmonary or cardiac comorbidities or exposed to invasive procedure and hemorrhage, and they transfuse with Hb less than 10 g/dL. The transfusions were not associated with any complications. Deferasirox was stopped in the consolidation phase during infusion of high dose methotrexate.

The main problem observed during the periods of induction and consolidation therapy was increased requirement of blood transfusions as well as repeated infections. During this period, the child received intensive chemotherapy, which caused bone marrow suppression

OUTCOME AND FOLLOW-UP

The child is still in complete remission and is in the continuation phase for standard risk (week 40).

DISCUSSION

We recently reported the first case from Egypt with βTM who developed ALL[2]. Herein, we report similarly the first patient from Egypt with βTI who developed ALL to highlight that the coexistence of malignancy and beta thalassemia is not rare.

A thorough review of the literature for previously reported cases of malignancies in patients with βTI revealed only one report in 2014 from Turkey of a 12-year-old boy with βTI who developed ALL[3]. Other previous reports of malignancies associated with βTI described non-Hodgkin's lymphoma[4-6], chronic myeloid leukemia[6,7], Hodgkin's lymphoma[5,6,8], hepatocellular carcinoma[9-13] and thyroid malignancies[14] (Table 1). To our knowledge, our patient is the second worldwide and the first from Egypt.

Although reported cases of malignancies associated with βTI are few, physicians should have a high index of suspicion of malignancies in this group of patients when they present with unexplained new symptoms or proposed symptoms and signs of malignancy.

Table 1 Previously reported cases of thalassemia intermedia who developed malignancies

Number of patients	Type of malignancy	Ref.
1	Acute lymphoblastic leukemia	[3]
1	Non-Hodgkin lymphoma (NHL)	[4]
3	NHL, Hodgkin lymphoma (HL)	[5]
10	NHL; HL; chronic myeloid leukemia (CML)	[6]
1	CML	[7]
1	HL	[8]
12	Hepatocellular carcinoma (HCC)	[9]
2	HCC	[10]
6	HCC	[11]
3	HCC	[12]
2	HCC	[13]
2	Thyroid cancer	[14]

Some patients have thalassemia major and others have thalassemia intermedia in references 5 and 6.

There should be special concern about management plans in these patients as they usually require more frequent blood transfusions, as the chemotherapy causes suppression of the bone marrow, which adds to baseline chronic hemolysis.

Because reported cases of malignancies in βTI are scarce, attempts to find a causal relationship between βTI and cancer development are beyond the scope of our report. We tried to search the literature for possible contributing factors, but those factors are not sufficient to allow us to draw any conclusions. Possible hypotheses regarding factors need to be addressed and validated by a larger prospective cohort with large control groups and multicenter worldwide studies. Indeed, an explanation of underlying factors for the development of malignancy in TI is likely multifactorial[15].

In a large multicenter study on thalassemia patients from Iran, the proportion of patients with cancer was higher in those with βTI than those with βTM; 0.54% and 0.20%, respectively[6]. It was suggested that bone marrow in βTM patients is suppressed by the regular transfusions, while it is very active with high turnover in those with βTI[6]. This can lead to a higher rate of DNA repair faults and mutations with subsequent higher rate of hematological malignancies[6].

Another potential factor is the prolonged use of hydroxyurea, and there are conflicting data regarding its carcinogenic potential. Hydroxyurea as an antimetabolite interferes with both DNA synthesis and repair mechanisms with later accumulation of mutations and subsequent chromosomal damage. Although no studies have yet investigated the relationship between hydroxyurea and the development of cancers in thalassemia, clinical concerns have been raised regarding its potential leukemogenic potential[7,15]. Other authors were against this assumption[6,16]. The BABYHUG clinical trial, which compared hydroxyurea with placebo treated controls, refuted this assumption and did not suggest any increased risk of genotoxicity[16].

Overall, there is no evidence to suggest an increased risk of carcinogenesis in patients with thalassemia with hydroxyurea and further studies will need to be designed to establish any potential relationship[14].

One more probable factor is that patients with βTI have milder disease than those with βTM, and fewer blood transfusions might lead to delayed diagnosis. Even if diagnosed, usually there is an underestimation of their iron overload problem. Sometimes the relatively mildly elevated ferritin in βTI, as compared to βTM, is underestimated and the true iron burden in these patients usually goes unnoticed, unchelated and unmonitored. Anemia, hypoxia and ineffective erythropoiesis suppress the expression of hepcidin by increasing expression of growth differentiation factor 15 and hypoxia-inducible transcription factors with resulting increase in intestinal iron absorption and, in turn, the problem of iron overload[13].

Long-standing iron overload with its deposition in different body organs, with the well-known association between excess iron and cancer development, can be a predisposing factor for all types of malignancies; through direct and indirect effects[13].

Iron can directly damage DNA by non-transferrin-bound iron, with the consequent inactivation of tumor-suppressor genes, such as *p53*, or their products. The indirect effects include the formation of reactive oxygen species, iron-induced lipid peroxidation, altered immune system with decreased immune surveillance, suppression of tumoricidal action of macrophages and alteration of cytokine activities. βTI patients usually survive longer than βTM patients with enough time for iron overload to develop[13].

Some authors have suggested that improved management protocols of thalassemia patients have led to increased survival, with most of them reaching adult age with the consequent occurrence of diseases associated with long life span like malignancies[5,7]. This assumption can partially explain other reports in elder patients but cannot explain our patient or the Turkish one, who are teenagers.

It has been suggested that the occurrence of malignancies in thalassemia patients could be a pure coincidence or a combination of genetic and environmental factors[3,7]?

CONCLUSION

In summary, whatever the pathogenesis of malignancies in thalassemias, the most important message is to alert physicians that they should suspect malignancies if their thalassemia patients develop suggestive symptoms and signs. Worsening anemia, leukocytosis, fever, bone-aches, lymphadenopathy and splenomegaly are signs to look for leukemias and other hematological malignancies.

REFERENCES

1 **Galanello R**, Origa R. Beta-thalassemia. *Orphanet J Rare Dis* 2010; **5**: 11 [PMID: 20492708 DOI: 10.1186/1750-1172-5-11]

2 **Sherief LM**, Kamal NM, Abdelrahman HM, Hassan BA, Zakaria MM. First report of acute lymphoblastic leukemia in an Egyptian child with β-thalassemia major. *Hemoglobin* 2015; **39**: 127-129 [PMID: 25707677 DOI: 10.3109/03630269.2015.1005747]

3 **Tuğcu D**, Karakaş Z, Gökçe M, Ağaoğlu L, Unüvar A, Sarıbeyoğlu E, Akçay A, Devecioğlu O. Thalassemia Intermedia and Acute Lymphoblastic Leukemia: Is it a Coincidental Double Diagnosis? *Turk J Haematol* 2014; **31**: 311-312 [PMID: 25330528 DOI: 10.4274/tjh.2014.0068]

4 **Chehal A**, Loutfi R, Taher A. Beta-thalassemia intermedia and non-Hodgkin's lymphoma. *Hemoglobin* 2002; **26**: 219-225 [PMID: 12403486 DOI: 10.1081/hem-120015025]

5 **Benetatos L**, Alymara V, Vassou A, Bourantas KL. Malignancies in beta-thalassemia patients: a single-center experience and a concise review of the literature. *Int J Lab Hematol* 2008; **30**: 167-172 [PMID: 18333849 DOI: 10.1111/j.1751-553X.2007.00929.x]

6 **Karimi M**, Giti R, Haghpanah S, Azarkeivan A, Hoofar H, Eslami M. Malignancies in patients with beta-thalassemia major and beta-thalassemia intermedia: a multicenter study in Iran. *Pediatr Blood Cancer* 2009; **53**: 1064-1067 [PMID: 19533641 DOI: 10.1002/pbc.22144]

7 **Alavi S**, Safari A, Sadeghi E, Amiri S. Hematological malignancies complicating β-thalassemia syndromes: a single center experience. *Blood Res* 2013; **48**: 149-151 [PMID: 23826586 DOI: 10.5045/br.2013.48.2.149]

8 **Jabr FI**, Aoun E, Yassine H, Azar C, Taher A. Beta-thalassemia intermedia and Hodgkin lymphoma. *Am J Hematol* 2006; **81**: 151 [PMID: 16432853 DOI: 10.1002/ajh.20478]

9 **Borgna-Pignatti C**, Vergine G, Lombardo T, Cappellini MD, Cianciulli P, Maggio A, Renda D, Lai ME, Mandas A, Forni G, Piga A, Bisconte MG. Hepatocellular carcinoma in the thalassaemia syndromes. *Br J Haematol* 2004; **124**: 114-117 [PMID: 14675416 DOI: 10.1046/j.1365-2141.2003.04732.x]

10 **Mancuso A**, Sciarrino E, Renda MC, Maggio A. A prospective study of hepatocellular carcinoma incidence in thalassemia. *Hemoglobin* 2006; **30**: 119-124 [PMID: 16540424 DOI: 10.1080/03630260500455565]

11 **Restivo Pantalone G**, Renda D, Valenza F, D'Amato F, Vitrano A, Cassarà F, Rigano P, Di Salvo V, Giangreco A, Bevacqua E, Maggio A. Hepatocellular carcinoma in patients with thalassaemia syndromes: clinical characteristics and outcome in a long term single centre experience. *Br J Haematol* 2010; **150**: 245-247 [PMID: 20433678 DOI: 10.1111/j.1365-2141.2010.08180.x]

12 **Fragatou S**, Tsourveloudis I, Manesis G. Incidence of hepatocellular carcinoma in a thalassemia unit. *Hemoglobin* 2010; **34**: 221-226 [PMID: 20524812 DOI: 10.3109/03630269.2010.485071]

13 **Maakaron JE**, Cappellini MD, Graziadei G, Ayache JB, Taher AT. Hepatocellular carcinoma in hepatitis-negative patients with thalassemia intermedia: a closer look at the role of siderosis. *Ann Hepatol* 2013; **12**: 142-146 [PMID: 23293206]

14 **Poggi M**, Sorrentino F, Pascucci C, Monti S, Lauri C, Bisogni V, Toscano V, Cianciulli P. Malignancies in β-thalassemia patients: first description of two cases of thyroid cancer and review of the literature. *Hemoglobin* 2011; **35**: 439-446 [PMID: 21797713 DOI: 10.3109/03630269.2011.588355]

15 **Halawi R**, Cappellini MD, Taher A. A higher prevalence of hematologic malignancies in patients with thalassemia: Background and culprits. *Am J Hematol* 2017; **92**: 414-416 [PMID: 28195443 DOI: 10.1002/ajh.24682]

16 **McGann PT**, Flanagan JM, Howard TA, Dertinger SD, He J, Kulharya AS, Thompson BW, Ware RE; BABY HUG Investigators. Genotoxicity associated with hydroxyurea exposure in infants with sickle cell

anemia: results from the BABY-HUG Phase III Clinical Trial. *Pediatr Blood Cancer* 2012; **59**: 254-257 [PMID: 22012708 DOI: 10.1002/pbc.23365]

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