CASE REPORT

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

Laila M Sherief, Esmael Goneim, Naglaa M Kamal, Amr Ibraheim, Fuad Alsofiani, Abdulraouf Alawur

ORCID number: Laila M Sherief 0000-0003-2088-4213; Esmael Goneim 0000-0003-1041-4488; Naglaa M Kamal 0000-0002-8535-3838; Amr Ibraheim 0000-0002-8607-1082; Fuad Alsofiani 0000-0001-8864-1037; Abdulraouf Alawur 0000-0002-6062-5649.

Author contributions: Sherief LM was involved in the conceptualization, data curation, investigation, project administration, supervision, validation, visualization, writing review and editing; Goneim I and Ibraheim A, performed data curation; Kamal NM was involved in literature review, writing-original draft, writing review and editing; Alsofiani F and Alawur A, performed literature review and writing-original draft; All authors had read and approved the final manuscript.

Informed consent statement: Written informed consent in the patient’s native language was obtained from her father.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE.

Abstract

BACKGROUND
β-thalassemia intermedia (βTI) is one of the hemoglobinopathies. It constitutes 10% of β-thalassemia cases yet being associated with a 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 βTI, 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 underlying the relationship between the two entities.

CONCLUSION
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

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.
Core tip: Cases have been reported for malignancies in patients of β-thalassemia major. However rare case reports 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.

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 10000 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 proved 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 seven 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 so 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 3.9 g/dL, white blood cell count of 250 × 10^9/L, and platelets 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 calculary cholecystitis and bilateral diffuse renal enlargement. Echocardiography showed mitral valve prolapse with trivial mitral regurgitation.

**MULTIDISCIPLINARY EXPERT CONSULTATION**

The pediatric haematologist/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 are CD10 positive, CD19 positive, CD34 positive, TDT positive, HLA-DR positive, CD13 positive, and CD33 positive.

Cytogenetic examination showed a normal karyotype with a DNA index of 1 and negative t(12,21), t(1,19), BCR-ABL, or 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. Thus, she was 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 4 times of high dose methotrexate (HDMTX), 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 who 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 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 as during this period the child received intensive chemotherapy which caused bone marrow suppression.

**OUTCOME AND FOLLOW-UP**

The child is still in complete remission while being now in the continuation phase for standard risk (week forty).

**DISCUSSION**

We have recently reported the first case from Egypt with β-thalassemia major (βTM) who developed ALL[1], herein we report similarly the first report from Egypt for a patient with βTI who developed ALL to highlight that the coexistence of malignancy and beta thalassemia is not rare.

A thorough look in literature for previously reported cases of malignancies in
patients with βTI revealed only one report in 2014 from Turkey on a 12 years old boy with βTI who developed ALL\(^6\). Other previous reports on malignancies associated with βTI described non-Hodgkin lymphoma\(^8\), chronic myeloid leukemia\(^9\), Hodgkin lymphoma\(^9\), hepatocellular carcinoma\(^9\), and thyroid malignancies\(^6\)\(^9\)\(^10\). To our knowledge our patient is the second worldwide and the first from Egypt.

Although reported cases of malignancies associated with βTI are few, it raises the attention of physicians to have 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.

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 the base line chronic hemolysis.

In spite that reported cases of malignancies in βTI are scarce which makes our trial to find causal relationship between βTI and cancer development beyond the scope of our report, but we tried to search literature for possible contributing factors. Those factors can’t rise to the level of conclusions and definitely need to be proved and validated by larger prospective cohort with large control groups multicenter worldwide studies addressing all possible hypotheses.

Indeed, the most practical logical thinking about that underlying factors for the development of malignancy in TI is being multifactorial\(^11\).

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\(^11\). They explained it by the fact that bone marrow in βTM patients is suppressed by the regular transfusions while it is very active with high turnover in those with βTI\(^11\). They suggested that this can lead to a higher rate of DNA repair faults and mutations with subsequent higher rate of hematological malignancies\(^11\).

Another potential factor is the prolonged use of hydroxyurea. Conflicting data are there 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, but clinically, concerns have been raised regarding its potential leukemogenic potential\(^12\)\(^13\). Other authors were against this assumption\(^6\)\(^12\). The BABYHUG clinical trial which compared hydroxyurea with placebo treated controls refuted this assumption and did not suggest any increased risk of genotoxicity\(^10\).

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\(^10\).

One more probable factor is that patients with βTI being having milder disease than those with βTM with fewer blood transfusions might lead to delayed diagnosis and even if diagnosed usually there is underestimation of their iron overload problem and sometimes the deceiving relatively mildly elevated ferritin as compared to βTM which has been shown to underestimate the true iron burden in βTI patient with ultimate fate that these patients accumulate iron but it 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 the resultant increased intestinal iron absorption and in turn adds to the problem of iron overload\(^13\).

The 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, and 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 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\(^15\)\(^16\). This assumption can partially explain other reports in elder patients, but it can’t work in our patient and the Turkish one who are teenagers.

Many authors suggested that the occurrence of malignancies in thalassemia patients could be a pure coincidence? or a combination of genetic and environmental factors?\(^15\)?
Table 1 Previously reported cases of thalassemia intermedia who developed malignancies

| Number of patients | Type of malignancy                                                                 | Ref. |
|--------------------|-------------------------------------------------------------------------------------|------|
| 1                  | Acute lymphoblastic leukemia                                                       | [1]  |
| 1                  | Non-Hodgkin lymphoma (NHL)                                                         | [4]  |
| 3                  | NHL, Hodgkin lymphoma (HL)                                                         | [5]  |
| 10                 | NHL; HL; chronic myeloid leukemia (CML)                                             | [4]  |
| 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.

CONCLUSION

We can sum up to a clear message that whatever the pathogenesis of malignancies in thalassemias, the most important message is to alarm physicians to have high index of suspicion for malignancies if their thalassemia patients develop suggestive symptoms and signs. Worsening anemia, leukocytosis, fever, bone-ache, lymphadenopathy and splenomegaly are alarming 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, Abdelafran HM, Hassan BA, Zakaria MA. 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. Tüçü D, Karakaş Z, Gökcen M, Ağaoğlu L, Unüvar A, Sarbeyoğlu 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. Chehab 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, Giri 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: 19532641 DOI: 10.1002/pbc.22144]
7. Afavi 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/bjr.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. Borgia-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 thalassaemia. Hemoglobin 2006; 30: 119-124 [PMID: 16870424 DOI: 10.1080/03630260500455565]
11. Restivo Pantalone G, Renda D, Valenza F, D’Amato F, Vitro S, 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: 20436368 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: 20324812 DOI: 10.3109/03630269.2010.485071]
Maakaron JE, Cappellini MD, Graziaedi 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]

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: 10.3109/03630269.2011.588555]

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]

McGann PT, Flanagan JM, Howard TA, Dertinger SD, He J, Kuhlarya 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; 58: 254-257 [PMID: 22012708 DOI: 10.1002/pbc.23365]
