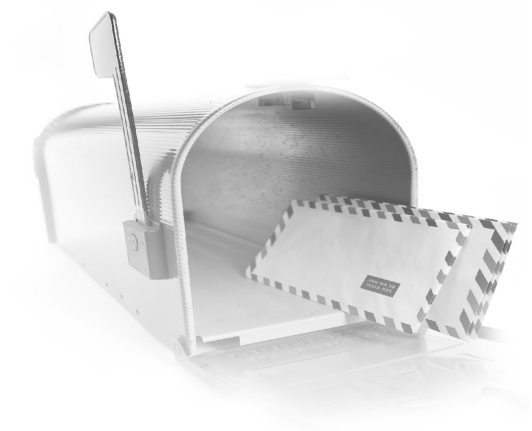

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Letters to the Editor

Hematological malignancies complicating β-thalassemia syndromes: a single center experience

TO THE EDITOR: Only few reports have addressed the occurrence of hematological malignancies in patients suffering from β-thalassemia. We herein report two patients with major and intermedia β-thalassemia who were complicated with Hodgkin's lymphoma and chronic myelogenous leukemia (CML) during the course of the disease, respectively. This report indicate that malignancies should be suspected and kept in mind in patients with β-thalassemia syndromes presenting with proposed signs and symptoms including unexplained lymphadenopathy, leukocytosis and splenomegaly.

β-thalassemia major is a genetic hemoglobinopathy characterized by point mutations of β-globin chain resulting in accumulation and deposition of unpaired β-globin chains in red blood cell (RBC). This causes severe hemolysis and ineffective hematopoiesis leading to severe anemia [1]. Currently the availability of proper care and appropriate treatment strategies including regular transfusions, allogeneic stem-cell transplantation, inducers of fetal hemoglobin, and precise iron chelation therapy with desferrioxamine (DFO) and/or deferiprone (DFP) have resulted in increased life expectancy and quality of life of the patients suffering from β-thalassemia major [2-4]. This increased life span increases the possibility of occurrence of other diseases such as malignancies. Although, previously malignancies were considered rare in β-thalassemia patients, but currently the number of malignancies reported in thalassemic patients is increasing [5-9]. We herein, report two patients with β-thalassemia major and intermedia who developed Hodgkin's lymphoma and chronic myelogenous leukemia (CML) during the course of the disease.

CASE 1

A 16-year-old girl with β-thalassemia major presented with painless bilateral cervical lymphadenopathies for 1 month. She had been on regular transfusion since 9 months of age and was HCV positive due to regular transfusions. Her parents were heterozygotes for β-thalassemia minor. Initial evaluations including complete blood count, biochemistry tests, Epstein barr virus infection (EBV) and toxoplasmosis studies were not conclusive. white blood cells and platelets were normal. serum ferritin levels of the patient were 3,200 ng/mL and 3,000 ng/mL at two occasions. She was receiving subcutaneous desferrioxamine at least 5 nights/week as iron chelation since 2.5 years of age. After about 3 weeks of persistent cervical lymphadenopathy, computerized tomography (CT) scan of the neck and chest was performed revealing bilateral cervical and upper anterior mediastinal lymph nodes with para-tracheal involvement .Abdominopelvic imaging was normal. An excisional lymph node biopsy was performed which was compatible with Hodgkin's lymphoma, nodular sclerosis subtype. Clinical staging revealed stage 2A (spleen was considered enlarged due to thalassemia since it was not a new finding). She was scheduled to receive systemic chemotherapy with 6 alternating cycles of MOPP/ABVD followed by radiotherapy and was off-therapy thereafter. Her mother also developed colon adenocarcinoma 6 years later and her brother (who was hematologically normal) died of brain tumor 8 years later. She also received antiviral treatments including α-interferon and ribavirin for HCV and changed to be negative. Fortunately, the patient is in remission for Hodgkin's lymphoma and still on regular blood transfusion after 10 years of follow-up.

CASE 2

A 13-year-old girl with β-thalassemia intermedia was referred to our clinic due to hyperleukocytosis (WBC: 154,000/mm^3). She was receiving hydroxyurea since 8 years of age and had been kept transfusion independent.

At presentation she had Hb 8.5–9 gr/dL, MCV 78 fL and MCH 20 pg. Hemoglobin electrophoresis revealed HbA 45%, HbF 51% and HbA2 4%. Spleen was palpated about 4cm below costal margin. Splenomegaly was evident as it was before. Due to the persistence of hyperleukocytosis (WBC: 50,000–150,000/mm^3) and aggravation of anemia, a bone marrow aspiration was performed which showed

hypercellular marrow with increased myeloid to erythroid ratio. Significant degrees of reticulin stain-measured fibrosis were noted accompanying marrow eosinophilia. The histopathological findings were in favor of chronic myelogenous leukemia (CML). Real time polymerase chain reaction examination for the detection of *BCR-ABL* translocation on bone marrow aspirate revealed positive reaction for 342 bp amplified product compatible with t(9;22)(q34;q11.2) translocation (Philadelphia chromosome). Treatment with Imatinib mesylate (Gleevec) was started at a dosage of 400 mg/day; however, she developed accelerated blastic crisis and proceeded towards acute myeloid leukemia (AML) and did not respond to chemotherapy regimens and thus died about 3 months after diagnosis.

DISCUSSION

In this brief article, we have presented two patients with thalassemia syndromes (β-thalassemia major and β-thalassemia intermedia) who developed hematologic malignancies (Hodgkin's lymphoma and CML) during the course of the disease. A thorough review of the literature reveals that only few cases of major β-thalassemia complicated with lymphoma has been reported [6, 8-10]. CML in a patient with β-thalassemia intermedia has not yet been reported. Sallam and colleagues [7] reported a patient with sickle cell/beta^0 thalassemia (β^S/β^0) who was complicated with CML. Several other studies have reported two patients with intermedia β-thalassemia who developed other hematological malignancies including non-Hodgkin lymphoma [11, 12].

The occurrence of hematological malignancies such as leukemia and lymphoma in thalassemia patients could be a pure coincidence or a combination of genetic and environmental factors. Previously, definite genetic link between thalassemia syndromes and lymphoma has been rejected by Quattrin and co-workers who reported comparable incidence of leukemia in patients with β-thalassemia and general population [12]. It was further reported by Zurlo and colleagues [13] that the most common cause of death in those with major β-thalassemia was heart disease, followed by infection, liver disease, and malignancy. Currently there are few reports available and thus we cannot comment on the relationship between malignancies and thalassemia syndromes.

In our report, immunomodulation due to multiple transfusions could be considered as a probable predisposing factor in development of Hodgkin's lymphoma in the patient with major β-thalassemia. In addition since she was HCV positive, it could be also proposed as a putative agent. Another probability is familial cancer syndromes in this case as a predisposing factor superimposed by acquired factors like immunmodulation due to transfusion and viral factors such as HCV infection. The probable mechanisms for occurrence of malignancy in the girl with β-thalassemia intermedia could be the same as general population or as a result of prolonged treatment with hydroxyurea for at least 4 years. There is also a report in the literature of a patient with sickle cell disease who developed acute myeloid leukemia after 2 years of hydroxyurea therapy [14]. The short interval between treatment with hydroxyurea and occurrence of leukemia more strongly suggests of therapy-related leukemia. Our first case had prolonged hyperferritinemia and also was receiving iron chelation treatment with desferrioxamine for a long time. The effects of iron over load and treatment with iron chelating agents could be another hypothesis for development of malignancies in these patients [15]; however, low incidence of malignancies still suggest coincidental occurrence of these conditions and none of these theories could be confirmed unless prospective cohort studies with large control groups are designed and performed.

In conclusion, malignancies should be suspected and kept in mind in the patients with β-thalassemia syndromes presenting with new onset signs and symptoms including lymphadenopathy, leukocytosis and splenomegaly.

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Pediatric chronic myeloid leukemia with B-cell lymphoid blast crisis at presentation

TO THE EDITOR: Chronic Myeloid Leukemia (CML) is a rare hematological malignancy accounting for less than 3% of pediatric and adolescent leukemias, with an annual incidence of approximately 1 per million children and young people aged <20 years [1]. The natural history and biology of pediatric CML is similar to those of adult CML and follows a tri-phasic pattern. Approximately 95% of children present with chronic phase CML (CML-CP) and the remainder present in the accelerated phase CML (CML-AP) or in blast crisis (CML-BC) [2]. CML-BC is defined by >20% blasts in the marrow or the presence of extra-medullary blast proliferation [3, 4]. Blast transformation of CML is lymphoid in 30% of cases and myeloid in the remaining 70%. We report the case of a 10-year-old boy who presented with a 6-week history of weight loss and left-sided upper abdominal pain. On examination, he was found to have substantial splenomegaly extending into the right iliac fossa. His full blood count showed a hemoglobin level of 6.6 g/dL, a platelet count of 148×10^9/L, and a total white cell count of 575×10^9/L. A differential count showed the following: blasts, 30%; promyelocytes, 6%; myelocytes, 24%; metamyelocytes, 11%; neutrophils, 7%; eosinophils, 9%; basophils, 3%; monocytes, 1%; and lymphocytes, 10% (Fig. 1). Flow cytometry of the blast population showed that the blasts expressed CD19, cyCD79a, CD10, HLA-DR, CD34, and TdT surface antigens. Chromosome analysis showed a t(9;22)(q34;q11) translocation consistent with a Philadelphia chromosome (Fig. 2A). Interphase fluorescence in situ hybridization (FISH) showed *BCR-ABL1* fusion signals in 90% of the nuclei (Fig. 2B). A minor breakpoint cluster region (210 kDa) was confirmed using RT-PCR. In the absence of a documented CML-CP, distinguishing between lymphoid blast crisis of CML and a Philadelphia chromosome-positive ALL can be difficult. A diagnosis of CML in B-cell lymphoid blast crisis rather than *de novo* precursor B-cell ALL was made because of the concurrent presence of basophilia, a predominance of metamyelocytes and myelocytes, and the p210 *BCR-ABL* transcript. The patient did not have any additional chromosomal anomalies associated with advanced phase CML and was negative for IgH rearrangement on FISH analysis.

The patient achieved a complete hematological response and a minor cytogenetic response following induction therapy comprising dexamethasone, vincristine, daunorubicin, asparaginase, and imatinib. Nonetheless, he subsequently died of idiopathic pneumonitis after allogeneic stem-cell transplantation.

The progression from CML-CP to CML-BC in the pre-tyrosine kinase era is well described, but CML-BC at presentation in children is extremely rare. The case reported here adds to the literature on the simultaneous presence of features of both lymphoblastic transformation and CML at presentation in the absence of cytogenetic clonal evolution. Further research into the biology of the aggressive phase of CML is required to develop novel targets to improve outcomes.

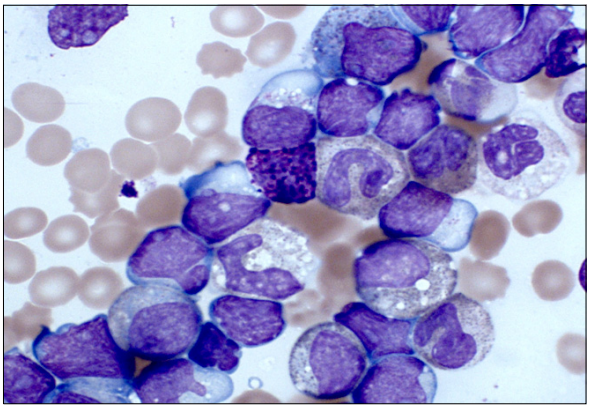

Fig. 1. Blood film demonstrating chronic myeloid leukemia in lymphoid blast transformation.