Open Access Case Report

A Challenging Case of Beta-Thalassemia Major with Increased Ring Sideroblasts in Bone Marrow

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Abstract

Symptomatic Beta-thalassemia is one of the most common genetic disorders worldwide. Early clinical manifestations are variable. Routine hematologic analysis is usually sufficient to diagnose the disease, but sometimes diagnosis can be more difficult. We present the case of a 1-year-old male patient who underwent a bone marrow biopsy with clinical signs of inherited bone marrow/erythropoietic failure. Numerous ringed sideroblasts were found in iron-stained smears raising the suspicion of congenital sideroblastic anemia. The child was later genetically diagnosed as beta-thalassemia major.

Keywords: Thalassemia distribution, beta-thalassemia disease, sideroblastic anemia

Introduction

β-Thalassemia is characterized by reduced or absent synthesis of β-globin chains within the HbA molecule, resulting in the accumulation of excess, unbound α-globin chains, which precipitates in erythrocyte precursors. This causes ineffective erythropoiesis and peripheral hemolysis in bone marrow and mature red blood cells. Approximately 1.5% of the world's population are carriers for β-thalassemia.[1] An often cited figure for Pakistan is approximately 100,000 transfusion-dependent thalassemic patients,[2] with a trait frequency ranging from 5–7%.[3]

The hematologic and clinical spectrum of beta-thalassemia disease varies from mild to severe including beta-thalassemia intermedia and beta-thalassemia major. Determining the factors that cause such diverse clinical manifestations is therefore of clinical importance, which is mainly due to mutational diversity.[4,5] Diagnosis of thalassemia requires few laboratory tests such as complete blood count (CBC), peripheral film and hemoglobin electrophoresis. Molecular tests may be used in certain conditions to detect mutations in the Beta and alpha-globin chain genes. It is also useful in determining thalassemia carrier status, although it is not routinely done. [6]

In this report, we present a case of a one-year old male child who underwent bone marrow aspiration with the clinical indication of congenital bone marrow/erythropoietic failure. Numerous ringed sideroblasts were noted on iron-stained smears. The child was later genetically diagnosed as Beta Thalassemia Major.

Case Report

Patient is one year old male child (6.6kgs) who presented with the complaints of progressive pallor for 6 months and history of repeated red cell transfusions during this period. He has been transfused 7 times during this 6 months period. Weaning was started at the age of 6 months. He was exclusively breast fed till 6 months of age. He is an unvaccinated child. Sitting without support was achieved at 11 months. The child cannot stand. He is a product of non-consanguineous marriage and there is no family history of thalassaemia. He has 1 elder sibling who is alive and healthy. On examination, there was pallor. Liver was palpable 2 cm below right costal margin, spleen was not palpable. There was no jaundice or lymphadenopathy. Blood CP showed TLC of 18000/ul, Hb 3.1g/dl MCV 85.9 fl and platelet count of 264,000/ul. Retics were 2.5%. No other investigation was available at the time of bone marrow biopsy. Bone marrow biopsy was planned as a workup for transfusion dependent anaemia to rule out congenital disorder. At the time of biopsy, his blood CP showed TLC of 13,000/ul, Hb 6.6g/dl(post transfusion) with MCV of 83.2fl, MCH 29.4pg, MCHC 35.4g/dl and platelet count of 231000/ul. Red cell morphology showed dimorphic blood picture with moderate anisopoikilocytosis along with microcytosis and hypochromasia, red cell fragmentation+, basophilic stippling +, spherocytes +, pappenheimer bodies and occasional target cells. (Figure 1) Reticulocytes were

3%. Differential leukocyte count was as follows: Neutrophils 45%, Lymphocytes 48%, Monocytes 2%, Eosinophils 5%. 11 nucleated RBCs/100 WBCs were seen. Bone marrow aspirate done from tibia showed hypercellular fragments and trails, erythroid hyperplasia with moderate megaloblastic change (Figure 2) and increased iron along with 35% ring sideroblasts (Figure 3, 4). In view of above mentioned findings and previous history of red cell transfusions, PCR for beta globin gene mutation was advised which showed compound heterozygous Fr 8-9+G/Cd 5- CT variant (Beta Thalassemia Major). The patient's parents were genetically counseled, advised family screening and were asked to register the patient in Thalassemia Centre for management.

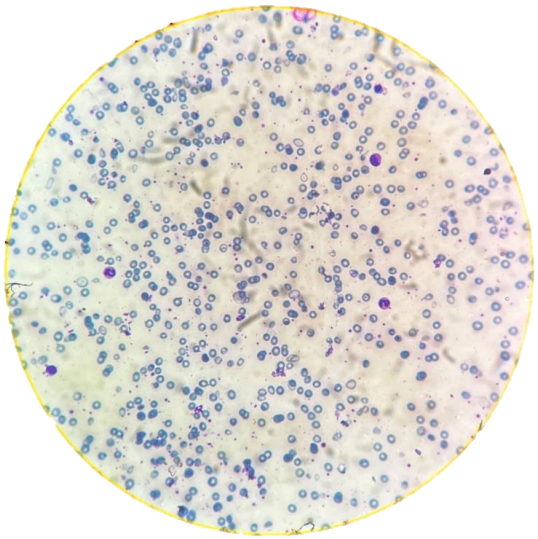

Figure 1. Peripheral Film (Giemsa Stain 400X)

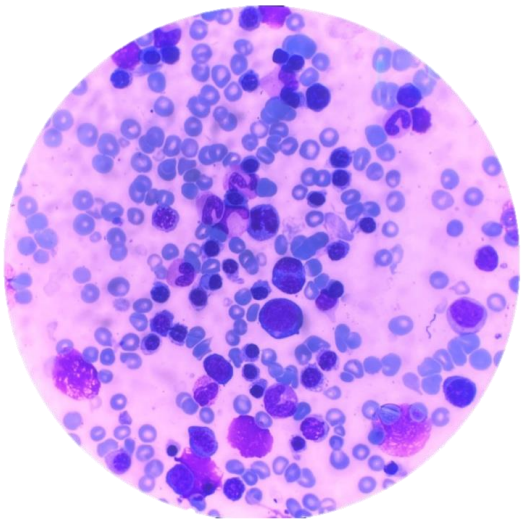

Figure 2. Bone Marrow Aspirate (Giemsa Stain 1000X)

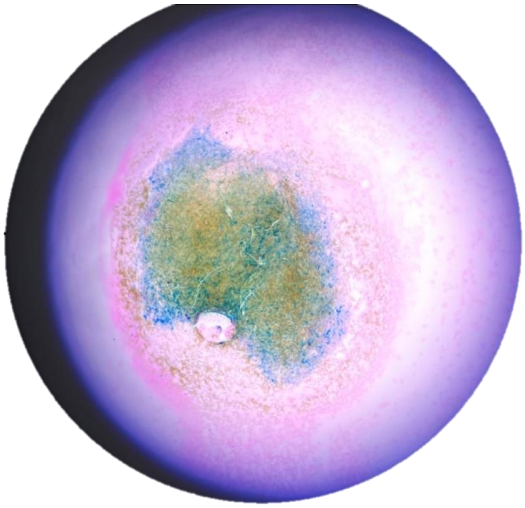

Figure 3. Perl's stain showing increased iron (100X)

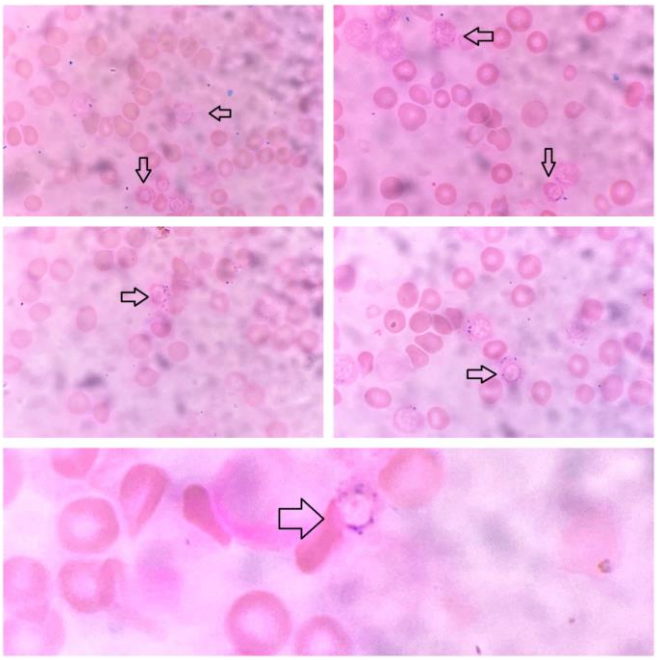

Figure 4. Perl's stain showing increased ring sideroblasts (1000X)

Discussion

Ring sideroblasts are defined as erythroid precursors having at least five siderotic granules encircling at least one-third of the circumference of cell nucleus (mitochondrial ferritin), after staining with Prussian Blue stain.[7,8] These can be observed in many clonal hematological and non-clonal disorders, including congenital sideroblastic anemia, alcoholism, drugs, copper deficiency, zinc excess and lead poisoning. [8] In literature, few cases of beta thalassemia have been reported with presence of increased ringed sideroblasts in bone marrow. Jeon et al. reported a 5

year-old Korean girl, mildly anemia, having iron overload, and heterozygous for an initiation codon missense β^0 allele. [9] Cattivelli et al. reported a series of thalassemia patients having a challenging diagnoses. Abnormal features contributing to delayed diagnosis were presentation at birth or early infancy, macrocytic anemia, only one carrier parent, or lack of the abnormal findings on routine electrophoresis. They presented a 1 year-old girl having a severe microcytic anemia at two months of age. Bone marrow aspiration performed at 8 months of age discovered many ringed sideroblasts. However, due to constantly elevated hemoglobin F and raised hemoglobin A2 in both parents, beta globin gene mutation was carried out and revealed the diagnosis of Beta-thalassemia major based on mutations: [IVS-I-1 (G>T)] and [IVS-I-6 (T>C)]. Another patient, a 35 year-old woman, at the age of 2 years developed hemolytic anemia with macrocytic red cell morphology. Many years later, on molecular analysis, she was found to have Beta-globin gene mutation with duplication of alpha-globin genes.[10] Our case was diagnosed late and bone marrow was performed initially due to atypical features such as absence of splenomegaly, and negative family history. Moreover, hemoglobin electrophoresis, which would have made the diagnosis early on could not be done due to history of regular transfusions since the age of 6 months.

Conclusion

The presence of ringed sideroblasts in patients with beta thalassemia is under-reported and unrecognized because in general, bone marrow aspiration is not performed routinely for diagnosis in these cases. This challenging case highlights that increased ringed sideroblasts can be found in beta thalassemia major. This may often complicate the case and may lead to mislabeling as congenital sideroblastic anemia, if not diagnosed by hemoglobin electrophoresis pre-transfusion or by molecular methods if transfused. Further studies are required to understand the pathophysiology behind the formation of ringed sideroblasts in beta thalassemias.

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