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Case Report

Beta-Thalassemia major with Gaucher disease

Mohammad Akbar Ibrahimi [a], Turyalai Hakimi [b,*], Sultan Ahmad Halimi [c]

[a] Department of Pediatrics, Kabul University of Medical Science, Maiwand Teaching Hospital, Kabul, Afghanistan
[b] Department of Pediatric Surgery, Kabul University of Medical Science, Maiwand Teaching Hospital, Kabul, Afghanistan
[c] Department of Pathology, Kabul University of Medical Science, Kabul, Afghanistan

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ABSTRACT

Introduction and importance: β-thalassemia major is an inherited disorder resulting from mutation or deletion of the beta-globin gene, causing a reduced beta-globin chain of hemoglobin. Gaucher's disease (GD) is a type of lysosomal storage disorder resulting from the deficiency of the glucocerebrosidase enzyme or storage of glucocerebrosides in the tissues. Coexistence of these two entities is very rare. The importance of reporting this case is that both medical conditions have overlapping clinical manifestations and the diagnosis of one will be mistaken for the other.

Case presentation: A 12-year-old child was brought to our pediatric department with complaints of abdominal distension, anemia, hepatosplenomegaly, and iron overload due to frequent blood transfusions. Initially, anemia and iron overload were treated with blood transfusion and iron chelation therapy along with management of congestive heart failure (CHF) followed by splenectomy. The patient's follow-up result was favorable.

Clinical discussion: β-thalassemia major is a genetic disorder that is prevalent in South Asian nations. GD, or lysosomal storage disease, is a rare medical condition requiring enzyme replacement therapy. Coexistence of both disorders is mostly missed where genetic screening is not available. β-thalassemia major is blood transfusion (BT) dependent, and the frequency of BT directly justifies the decision for splenectomy due to splenomegaly and iron overload.

Conclusion: Our report highlights the similarities of Beta thalassemia major and GD due to overlapping clinical manifestations, therefore this is wise to do all relevant clinical investigations for the purpose of definite diagnosis and proper treatment of both medical conditions.

1. Introduction

Thalassemia is a common blood disorder caused by insufficient or absent β-globin chain of hemoglobin (Hb) [1,2]. Adult human hemoglobin (HbA) comprises of two α and two β globin chains encoded by the α-globin gene (chromosome 16) and β-globin gene (chromosome 11), respectively [3]. In β-thalassemia, lack of synthesis or reduced production of β-globin and continued production of α-globin chains within the developing red blood cells (RBCs) results in the chain imbalance, leading to the production of microcytic hypochromic (RBCs) in the bone marrow.

Excess of α-globin causes RBCs membrane oxidative damage, leading to apoptosis [4]. Therefore, RBCs massive destruction results in anemia in β-thalassemia. Around 1.5% of the world populations (80–90 million people) are β-thalassemia carriers [2]. Patients with β-thalassemia suffer from chronic hemolytic anemia and require blood transfusion on a regular basis beginning in childhood. Choronic blood transfusion therapy is typically combined with iron chelation therapy (ICT) to prevent iron overload complications, such as liver disease, cardiac morbidity and endocrine disorders [5–7].

Gaucher's disease (GD) is a medical condition characterized by a deficiency of the lysosomal enzyme of glucocerebrosidase due to mutation in the gene of GBA1 on chromosome 1. The accumulation of glucocerebroside, and glucosylsphingosine in the monocyte-macrophage system, give a Gaucher appearance to the cells [8]. As a result, GD manifests as hepatosplenomegaly, thrombocytopenia, anemia, neurological impairment, and skeletal involvement [9]. The estimated worldwide frequency of GD is 1/50:000–1/100:000 [10].

Abbreviations: GD, Gaucher disease; CHF, Congestive heart failure; HbA, Adult human hemoglobin; RBC, Red blood cell; CXR, Chest x-ray; ICT, Iron chelation therapy; CTR, Cardiothoracic Ratio; BT, Blood transfusion.

* Corresponding author.
E-mail address: dr.turyalaihakimi@gmail.com (T. Hakimi).

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According to the literature, different hemoglobinopathies coexist with storage disorders [11,12]. But the coexistence of these two medical conditions is rare.

2. Case presentation

A 12-year-old child was brought by his parents due to abdominal distention, anemia, pedal edema, abdominal visceromegaly (hepatosplenomegaly) and high grade fever to the pediatric service of Maiwand teaching hospital. The patient was born (term and normal) to a consanguineous couple with no history of the aforementioned or other medical problems. Ante-natal history was unremarkable and all post-natal vaccinations were done.

According to the patient's parents' information, the child was healthy until 6 months of age, but started to become anemic after that. They consulted different physicians (mostly pediatricians) and received a variety of treatments for the problem. For definite diagnosis and better treatment, they took their child outside the country, where technical facilities were available. There, the patient was fully screened with the genetic test, confirming thalassemia major. Since then, their child received regular blood transfusions until referral to our teaching hospital.

On admission to the pediatric ward, the patient's main complaints were abdominal distention, weakness, and lethargy for two months. On physical exam, pallor, pedal edema, splenomegaly, tachycardia, and tachypnea were noted. CT-Scan image showed heptosplenomegaly (Fig. 1). Blood tests revealed moderate anemia with Hb of around 7gr/dl and ferritin level of around 3000. The chest X-ray showed cardiomegaly (Fig. 2), and with echocardiography, the patient's ejection fraction was 40%. Initially, the patient was admitted with the provisional diagnosis of thalassemia and congestive heart failure (CHF). The pediatric team administered two points of packed red cells (PRC) and iron chelation therapy with the initiation of defroxamine at a dose of 50 mg/kg/dose once a day, preferably at night, with appropriate anti-microbial therapy for one week.

Given the patient's marked splenomegaly and the frequency of blood transfusions, both pediatrics and pediatric surgery departments discussed and agreed on the patient's splenectomy for two reasons: alleviation of hemosiderosis and extension of blood transfusion time. The patient was referred to the pediatric surgery department and admitted. Following preparation, the patient underwent splencetomy (Fig. 3 A, B&C) and the specimen was sent for histopathology analysis, which revealed GD (Fig. 4A and B). The operation ended uneventfully, and following 74 post-operative hours, the patient was discharged with proper advice (regular consultation with our department of pediatrics).

During two months of follow-up, the patient's transfusion time was prolonged, but due to seasonal infections in the winter, he got a chest infection and came to the hospital complaining of cough and fever with

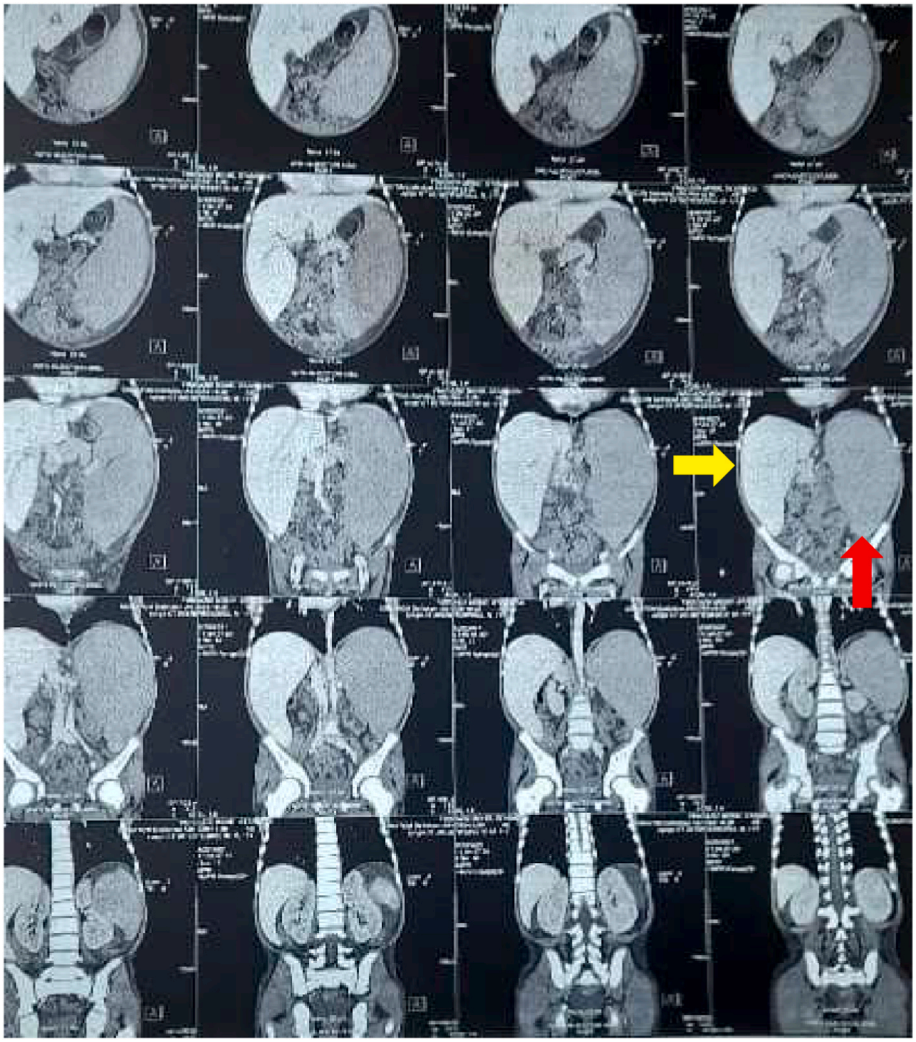

Fig. 1. CT-Scan coronal view, showing hepatosplenomegaly (Yellow arrow hepatomegaly, Red arrow splenomegaly). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

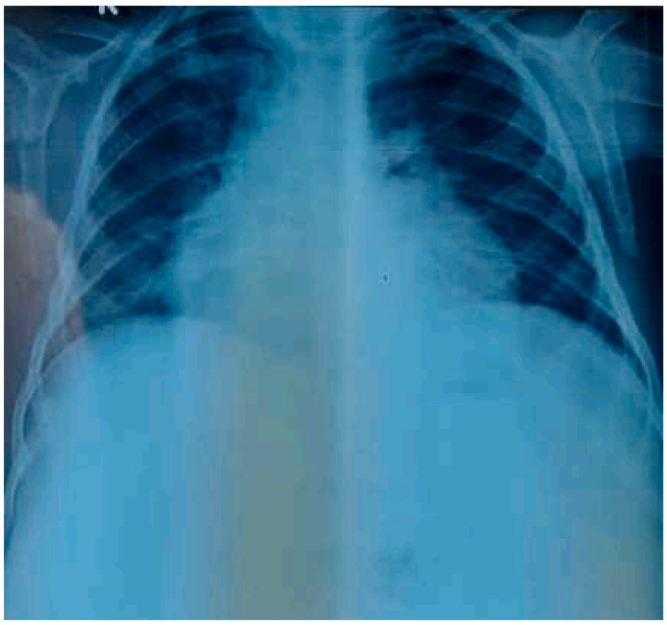

Fig. 2. Chest x-ray (CXR) showing cardiothoracic ratio (CTR) around 0.7 confirming cardiomegaly.

mild anemia. After the patient's evaluation, the patient was treated with blood transfusion and proper anti-microbial therapy. The patient's condition has improved, and he is doing well now.

3. Discussion and conclusions

β -Thalassemias are a diverse group of inborn hemoglobinopathies characterized by a fault in the globin chain of hemoglobin. There is an imbalance in the production of α- and non–α-globin in the compound heterozygous or homozygous forms, resulting in ineffective erythropoiesis and reduced production of normal hemoglobin (HBA) [13]. β-Thalassemia sufferers have severe chronic hemolytic anemia and are blood transfusion dependent from early childhood [13–15].

People of Mediterranean, Middle Eastern, and Asian descent have the highest prevalence of β-thalassemia mutations [16]. β-Thalassemia is classified by its clinical and laboratory findings into three clinical types. β-Thalassemia minor, also called a carrier or trait, is a heterozygous state that is asymptomatic with mild anemia. β-thalassemias intemedia and major are referred to as heterozygous states, where anemias are more severe. Clinically, β-thalassemia major is transfusion dependent, whereas β-thalassemias intermedia is not. The prevalence of β-thalassemia is 80–90 million carriers, or around 1.5% of the global population [17].

Ineffective erythropoiesis may lead to severe anemia, erythroid hyperplasia with bone marrow expansion, and extramedullary hematopoiesis. The bone marrow expansion causes bone deformities in facial

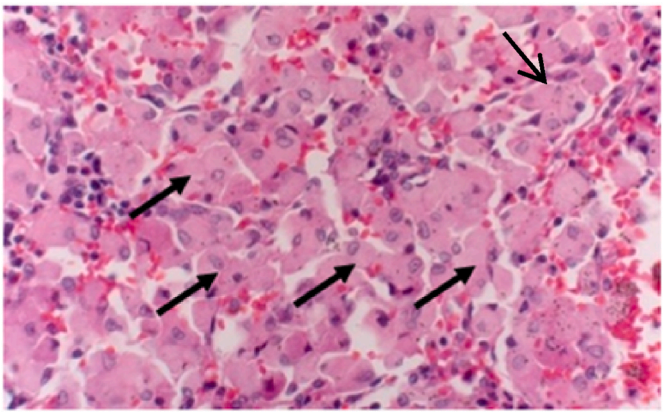

Fig. 4A. Microscopic examination revealed numerous enlarged macrophages at the higher magnification under H&E stained slides of the patient spleen.

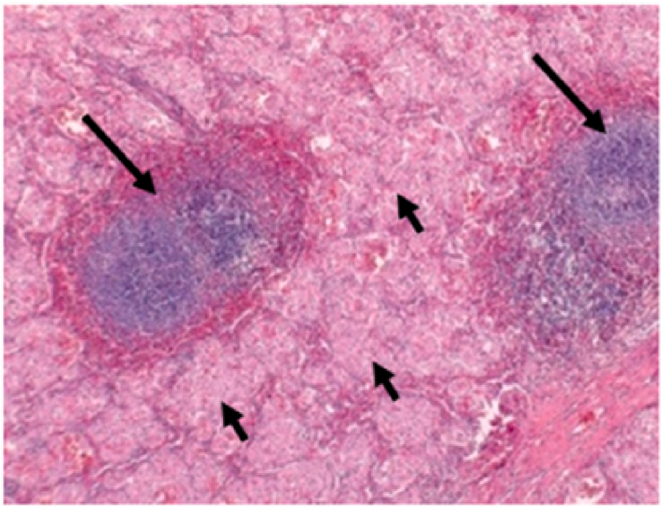

Fig. 4B. The spleen red pulp is occupied with enlarged macrophages (small arrows), while white pulp still recognizable (long arrow). Similar tissue macrophages are seen in many other organs in these patients. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

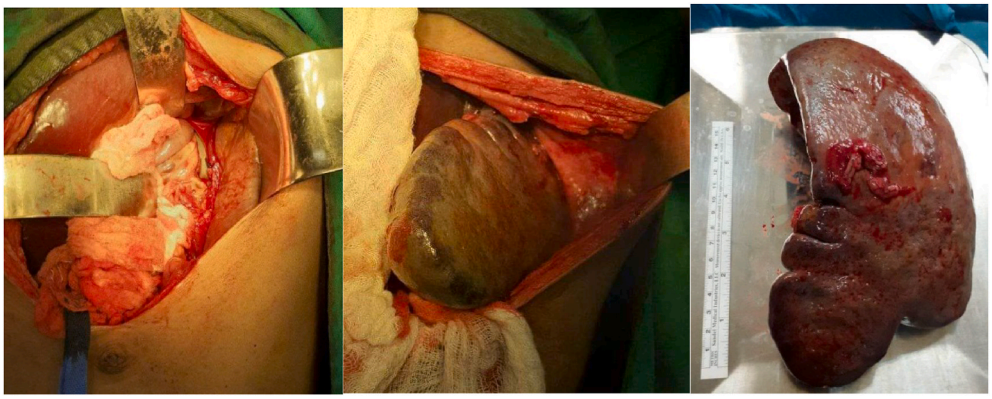

Fig. 3. (A). Exposure of spleen, (B). Mobilization of spleen, (C). Removed spleen.

bones (frontal bossing and maxillary protrusion). The inhibition of hepcidin production by biochemical signaling from bone marrow expansion involving the bone morphogenetic protein (BMP) pathway causes iron hyperabsorption [18]. Incompletely treated and transfusion-dependent patients are at risk for end-organ damaging iron overload. Continuing hemolysis and hepatosplenomegaly from extramedullary hematopoiesis may lead to thrombocytopenia and hepatic dysfunction. Common clinical manifestations of β-thalassemia are fatigue, feeding problems, pale skin, irritability, slow growth, and abdominal distension. Additionally, beta-thalassemia is common in consanguineous marriages [19,20]. Clinically, β-thalassemia is diagnosed by red blood cell indices, peripheral blood smear, qualitative and quantitative hemoglobin analysis through electrophoresis, and more certainly through genetic analysis by PCR-based procedures [19]. Regular blood transfusions and chelation therapy are used to treat β-thalassemia.

Gaucher's Disease (GD) is an autosomal recessive genetic disorder in which a sphingolipid glucocerebroside gathers in cells and different body organs due to a lack of the lysosomal enzyme "beta-glucocerebrosidase" [21]. GD manifests as hepatosplenomegaly, bone, cardiac, neurological, and ocular involvement [22]. Type 1 GD is most common (95%) in western countries, with symptoms of hepatosplenomegaly, fatigue, and bone problems, but no neurological impairment. Type 2 commonly occurs in infants and manifests with neurological problems, while type 3 (juvenile or subacute neurological GD) is a clinical type which is a transitional form between types 1 and 2 [23]. However, a broad spectrum of phenotypes are observed in GD, but hematologic manifestations are similar to thalassemia, resulting in a diagnostic dilemma [24].

The diagnosis of GD is made through a physical exam, laboratory tests, and genetic mutation analysis that reveals a deficient enzyme. Additionally, diagnosis of GD is given by observation of Gaucher's cells on bone marrow aspirate as having a "wrinkled tissue paper appearance" [22]. Treatment of GD falls into two categories: enzyme replacement therapy with two FDA-approved agents, Cerezyme (imiglucerase) and VPRIV (velaglucerase alfa) and substrate reduction therapy with Eliglustat and Miglustat. Eliglustat does not cross the blood-brain barrier [25,26], and Miglustat is used only in adults.

Our patient was previously diagnosed with β-thalassemia using genetic tests outside the country and treated with regular blood transfusions until the referral to our pediatric department with marked visceromegaly. Similar to the literature, our patient was born to a consanguineous couple, but contrary to the literature, our patient had no bone deformitiy. Iron overload due to repeated blood transfusions (every 10 days) and anemia were treated. Splenectomy was conducted by the pediatric surgery team and following surgery, the period of frequent blood transfusion was reduced, preventing iron overload. The GD diagnosis was made by histopathology specimen analysis in our university pathology department. Enzyme replacement therapy is not available here, or in our neighboring countries. The patient is following-up and is doing well now. Definite diagnosis and proper treatment are the main factors for improving the quality of life in patients suffering from β-thalassemia associated with Gaucher's disease.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Declaration of the competing interest

The authors declare that they have no known competing financial interests of personal relationships that could have appeared to influence the work reported in this paper.

Registration of research studies

Not applicable.

Ethical approval

No ethical approval was necessary.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Authors' contributions

Turyalai Hakimi (TH) conceptualized the manuscript. TH and Mohammad Akbar Ibrahimi (MAI) designed the study. TH and MAI wrote the original draft and edited the manuscript. TH performed the procedure. Sultan Ahmad Halimi (SAH) contributed to the histopathology analysis of the specimen. TH, AMI and SAH supervised the entire study process. All authors read and approved the final manuscript.

Provenance and peer review

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Guarantor

The corresponding author is the guarantor of the work, having the responsibility of data access and controlling the decision to publish.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ijso.2022.100460.

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