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**Case Report**

# Case report of a 19-year-old patient with β-thalassemia major, type 1 diabetes mellitus, osteoporosis and other major complications

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## ABSTRACT

This case report presents a detailed clinical profile of a 19-year-old male with β-thalassemia major, highlighting the multi-system complications associated with long-term disease management and chronic transfusion therapy. Diagnosed at one year of age due to symptoms including poor feeding, irritability, developmental delays, and failure to thrive, the patient's haemoglobin electrophoresis showed markedly elevated HbF levels, confirming β-thalassemia major. Over the years, the patient has undergone regular transfusions and a splenectomy at age seven to address hypersplenism. Family screening in 2014 identified β-thalassemia trait in both parents and three siblings, prompting genetic counselling. In 2020, the patient developed diabetic ketoacidosis, presenting with hyperglycaemia and ketonuria, and was subsequently diagnosed with type 1 diabetes mellitus, managed with insulin therapy. By 2023, he exhibited signs of iron overload, with MRI showing iron deposition across multiple organs and serum ferritin levels exceeding 2000 ng/mL. Additional findings included hepatomegaly, mild pleural effusion, thyroid dysfunction, and osteoporosis confirmed by bone mineral density testing. Current management includes oral deferasirox for iron chelation, calcium and vitamin D supplementation, folic acid, and insulin therapy tailored to his glucose needs.

**Keywords:** Thalassemia major, β-thalassemia, Osteoporosis, Blood transfusion, Hemoglobinopathies, Thalassemia minor, Thalassemia intermedia

## INTRODUCTION

Beta-thalassemias are inherited blood disorders caused by impaired synthesis of beta-globin chains in haemoglobin, leading to varying degrees of anaemia and symptoms. The global incidence of symptomatic cases is about 1 in 100,000. This condition encompasses a spectrum of hemoglobinopathies, primarily classified into three forms: thalassemia major, intermedia, and minor.[1]Thalassemia major, the most severe form, manifests in the first two years of life with severe anaemia, requiring regular RBC transfusions. Inadequate transfusion treatment can lead to growth retardation, jaundice, hepatosplenomegaly, skeletal deformities, and extra medullary masses. Chronic transfusions can cause iron overload, resulting in complications like diabetes, delayed sexual development, and liver and heart disease.[2] Beta-thalassemia is primarily caused by point mutations or, less commonly, deletions in the beta-globin gene on chromosome 11, leading to reduced (β+) or absent (β0) beta-chain synthesis.[3] This condition is often associated with iron overload, particularly affecting the pancreas, which impairs insulin secretion and increases insulin resistance, raising diabetes risk.

Family history, lifestyle, obesity, gender, and age further elevate diabetes susceptibility in beta-thalassemia patients.[4] Osteoporosis is a prevalent complication in β-thalassemia major (β-TM), increasingly noted these days due to advancement in diagnostic modalities. Even with proper transfusion and iron chelation, patients with β-TM often face low bone density and a heightened fracture risk,

leading to reduced quality of life and increased morbidity.[5] Thalassemia diagnosis relies on hematologic and molecular genetic testing, with genetic counselling and prenatal diagnosis often recommended. Treatment for thalassemia major typically involves regular RBC transfusions, iron chelation, and managing complications from iron overload in some cases, splenectomy may be necessary. Currently, bone marrow transplantation is the only definitive cure. Advances in transfusion, iron chelation, and bone marrow transplantation over the past 20 years have significantly improved the prognosis for individuals with beta-thalassemia. However, cardiac disease remains the leading cause of mortality in patients with iron overload.[6]

## CASE REPORT

This study was conducted in the department of obstetrics A 19-year-old male with a history of β-thalassemia major, diagnosed at the age of one, presented to our hospital for a routine follow-up. His initial diagnosis was triggered by symptoms of poor feeding, delayed milestones, irritability, and inadequate weight gain observed in 2006. Screening at that time revealed a haemoglobin level of 4 g/dl (Table 01), with a peripheral blood smear showing marked anisocytosis, poikilocytosis, and a mix of microcytic and macrocytic cells alongside polychromasia.

**Table 1: Complete haematological assessment.**

| Parameters | Results | Reference range |
|---|---|---|
| **WBC** | 5.2 ×10^3/ul | 4.0–11.0 |
| **Lymph** | 2.2×10^3/ul | 2.0-9.0 |
| **Mid** | 0.6×10^3/ul | 0.1–4.0 |
| **Gran** | 2.3×10^3/ul | 2.0-9.0 |
| **Lymph%** | H 41.9 % | 20.0–40.0 |
| **Mid%** | H 18.0 % | 3.0–7.0 |
| **Gran%** | L 40.1 % | 50.0–70.0 |
| **HGB** | L 4.0 g/dl | 11.5–14.5 |
| **RBC** | L 1.65×10^6/ul | 4.00–5.40 |
| **HCT** | L 16.6 % | 35.0–49.0 |
| **MCV** | L 64.6 fl | 77.0–91.0 |
| **MCH** | L 24.6 pg | 25.0–32.0 |
| **MCHC** | H 37.7 g/dl | 31.5–34.5 |
| **RDW-CV** | 18.2 % | 11.5–14.5 |
| **RDW-SD** | 54.1 fl | 35.0–56.0 |
| **PLT** | 155×10^3/ul | 150–450 |
| **MPV** | 10.8 fl | 7.0–11.0 |
| **PDW** | L 14.7 | 15.0–17.0 |
| **PCT** | 0.167 % | 0.108–0.282 |

**Table 2: Other investigations including TFT and serum ferritin levels.**

| Parameters | 2016 | 2023 | 2024 | Reference range |
|---|---|---|---|---|
| **T3** | 108.86 | 0.73 | 60.13 | 82-213 ng/dl |
| **T4** | 5.64 | 4.59 | 3.21 | 5.6-11.7 ug/dl |
| **TSH** | 3.458 | 2.0 | 2.64 | 0.45-4.5 uIU/ml |
| **Serum ferritin** | 3942 | 2153 | 2954 | 28-397 ng/ml |

**Table 3: HBA, HBF, HBA2 levels of other family members depicting familial association.**

| Parameters (2014) | Age (in years) | HbA % | Hbf % | HbA2 % |
|---|---|---|---|---|
| **Patient** | 8 | 83.2 | 3.1 | 5.5 |
| **Mother** | 30 | 82.6 | 3.6 | 5.3 |
| **Father** | 38 | 82.1 | 2.7 | 5.3 |
| **Sibling 1 (male)** | 20 | 84.4 | 1.0 | 5.2 |
| **Sibling 2 (female)** | 17 | 83.8 | 1.0 | 5.2 |
| **Sibling 3 (male)** | 4 | 84.8 | 1.8 | 5.6 |
| **Reference Range** | - | 96-98 | 0.5- 0.8 | 1.5-3.2 |

Platelets were adequate. Agarose gel electrophoresis of haemoglobin demonstrated HbA at 8.7% (reference range, 96.0-99.0%), HbF at 89.5% (reference range <2.0%), and HbA2 at 1.8% (reference range <3.5%), which confirmed a diagnosis of β-thalassemia major. Sickling test was negative.

The patient was subsequently managed with regular blood transfusions and supportive care as required. In 2011, a splenectomy was performed under general anaesthesia. Both direct and indirect Coombs tests were negative, and serological testing for transfusion-transmissible infections was non-reactive.

During a follow-up in 2014, the patient's family members underwent haemoglobin electrophoresis, which identified β-thalassemia trait in the mother, father, and three siblings but they were asymptomatic.

They were provided genetic counselling to understand potential future risks. HbA, HbF and HBA2 of patient's family members is given in the Table 03.

In 2020, the patient presented to the emergency department with a syncopal episode. Initial evaluation revealed a random blood glucose level of 452 mg/dl, HbA1c of 17.4%, urine ketones at +3, and an ABG profile with pH-6.79 (normal: 7.35-7.45), Pco2-25.70 (normal 35-48), Po2- 149 (normal: 83-108) suggestive of diabetic ketoacidosis (DKA).

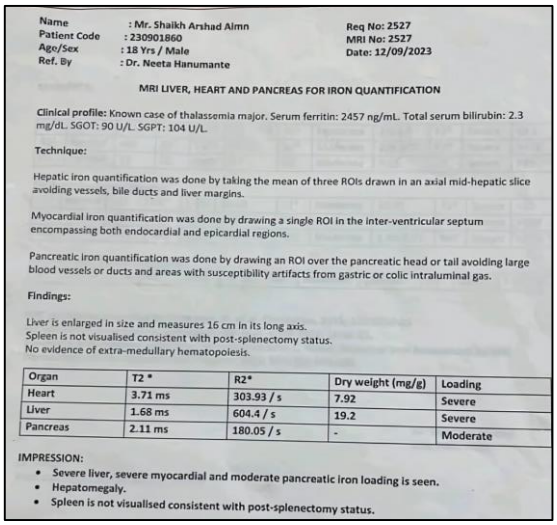
He was managed under close observation and started on insulin therapy, which has been continued as part of his management for type 1 diabetes mellitus.

In 2023, during a follow-up, the patient was found to have an abnormal thyroid profile (Table 2), hepatomegaly, and mild right-sided pleural effusion on ultrasonography. MRI findings of iron quantification of organs showed significant iron deposition across various organs, attributed to chronic transfusion therapy (Figure 1).

Bone mineral density assessment identified osteoporosis (Figure 2). Serum ferritin levels were noted to be >2000 ng/ml (Table 2), indicative of iron overload. Some other accidental findings included raised IgE-664.7 ng/ml (normal range is 3.6-480 ng/ml).

The patient's current management includes oral deferasirox (100 mg daily) for iron chelation, calcium and vitamin D supplementation (Calcimax 500 mg daily), folic acid (Folvite 5 mg daily), and an insulin regimen comprising a premixed insulin twice daily along with Actrapid adjusted based on glucose levels.

He has been advised to continue this regimen for three months, with indicated blood transfusions every 21 days, with a follow-up planned thereafter to monitor treatment response and manage any further complications.



Name : Mr. Shaikh Arshad Almn
Patient Code : 230901860
Age/Sex : 18 Yrs / Male
Ref. By : Dr. Neeta Hanumante

Req No: 2527
MRI No: 2527
Date: 12/09/2023

MRI LIVER, HEART AND PANCREAS FOR IRON QUANTIFICATION

**Clinical profile:** Known case of thalassemia major. Serum ferritin: 2457 ng/mL. Total serum bilirubin: 2.3 mg/dL. SGOT: 90 U/L. SGPT: 104 U/L.

**Technique:**

Hepatic iron quantification was done by taking the mean of three ROIs drawn in an axial mid-hepatic slice avoiding vessels, bile ducts and liver margins.

Myocardial iron quantification was done by drawing a single ROI in the inter-ventricular septum encompassing both endocardial and epicardial regions.

Pancreatic iron quantification was done by drawing an ROI over the pancreatic head or tail avoiding large blood vessels or ducts and areas with susceptibility artifacts from gastric or colic intraluminal gas.

**Findings:**

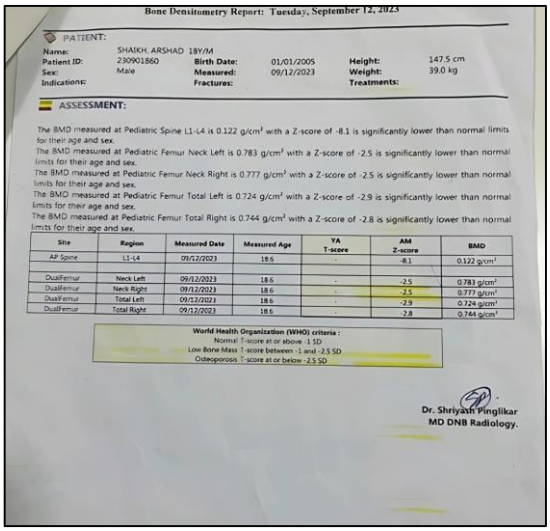
Liver is enlarged in size and measures 16 cm in its long axis.
Spleen is not visualised consistent with post-splenectomy status.
No evidence of extra-medullary hematopoiesis.

| Organ | T2 * | R2* | Dry weight (mg/g) | Loading |
|---|---|---|---|---|
| Heart | 3.71 ms | 303.93 / s | 7.92 | Severe |
| Liver | 1.68 ms | 604.4 / s | 19.2 | Severe |
| Pancreas | 2.11 ms | 180.05 / s | - | Moderate |

IMPRESSION:

- Severe liver, severe myocardial and moderate pancreatic iron loading is seen.
- Hepatomegaly.
- Spleen is not visualised consistent with post-splenectomy status.

**Figure 1: MRI quantification.**



Bone Densitometry Report: Tuesday, September 12, 2023

PATIENT:

Name: SHAIKH, ARSHAD 18Y/M
Patient ID: 230901860
Sex: Male
Indications:
Birth Date: 01/01/2005
Measured: 09/12/2023
Fractures:
Height: 147.5 cm
Weight: 39.0 kg
Treatments:

ASSESSMENT:

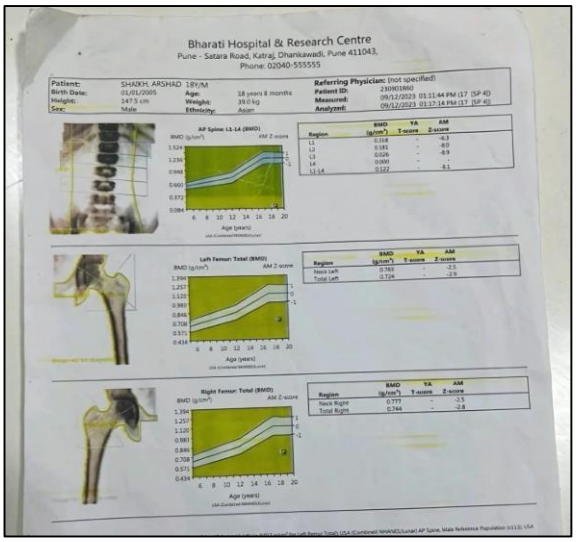
The BMD measured at Pediatric Spine L1-L4 is 0.122 g/cm² with a Z-score of -8.1 is significantly lower than normal limits for their age and sex.
The BMD measured at Pediatric Femur Neck Left is 0.783 g/cm² with a Z-score of -2.5 is significantly lower than normal limits for their age and sex.
The BMD measured at Pediatric Femur Neck Right is 0.777 g/cm² with a Z-score of -2.5 is significantly lower than normal limits for their age and sex.
The BMD measured at Pediatric Femur Total Left is 0.724 g/cm² with a Z-score of -2.9 is significantly lower than normal limits for their age and sex.
The BMD measured at Pediatric Femur Total Right is 0.744 g/cm² with a Z-score of -2.8 is significantly lower than normal limits for their age and sex.

| Site | Region | Measured Date | Measured Age | YA T-score | AM Z-score | BMD |
|---|---|---|---|---|---|---|
| AP Spine | L1-L4 | 09/12/2023 | 18.6 | - | -8.1 | 0.122 g/cm² |
| DualFemur | Neck Left | 09/12/2023 | 18.6 | - | -2.5 | 0.783 g/cm² |
| DualFemur | Neck Right | 09/12/2023 | 18.6 | - | -2.5 | 0.777 g/cm² |
| DualFemur | Total Left | 09/12/2023 | 18.6 | - | -2.9 | 0.724 g/cm² |
| DualFemur | Total Right | 09/12/2023 | 18.6 | - | -2.8 | 0.744 g/cm² |

World Health Organization (WHO) criteria :
Normal T-score at or above -1 SD
Low Bone Mass T-score between -1 and -2.5 SD
Osteoporosis T-score at or below -2.5 SD

Dr. Shriyash Pinglikar
MD DNB Radiology.

**Figure 2: BMD scans.**



Bharati Hospital & Research Centre
Pune - Satara Road, Katraj, Dhankawadi, Pune 411043.
Phone: 02040-555555

**Figure 3: BMD scans.**

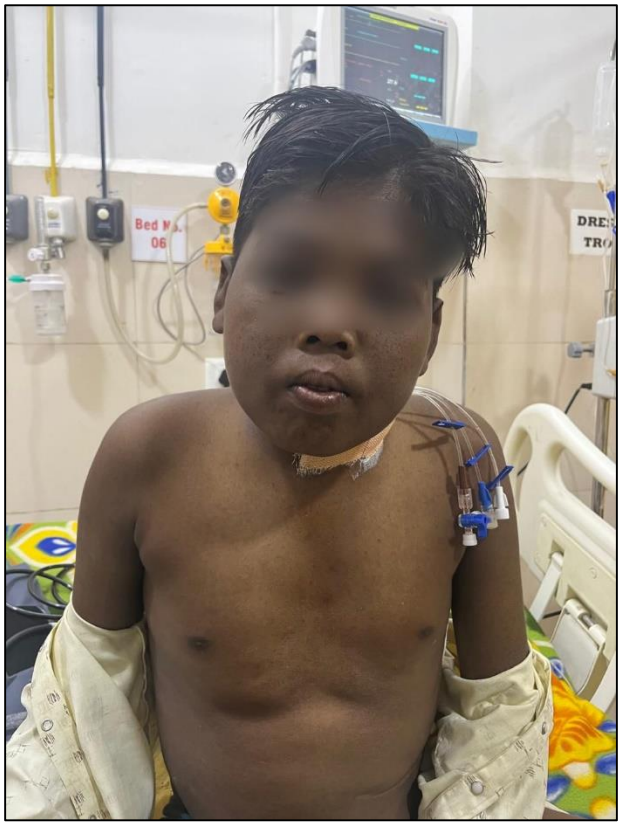


**Figure 4: Patient with thalassemic features.**

## DISCUSSION

The clinically relevant variants of β-thalassemia, β-thalassemia major and β-thalassemia intermedia, are characterized by either a complete lack or reduction in the synthesis of the beta globin chain, a crucial component of haemoglobin. Patients with β-thalassemia major typically present between six and 24 months of age with symptoms including severe anaemia-induced pallor, impaired weight gain, growth retardation, mild jaundice, and hepatosplenomegaly. Additional clinical features may encompass feeding difficulties, recurrent diarrhea, irritability, and frequent episodes of fever.[7]

β-thalassemia follows an autosomal recessive inheritance pattern. When both parents are heterozygous carriers of a pathogenic variant in the HBB gene, each sibling of an affected individual has a 25% probability of being affected, a 50% chance of being a (typically) asymptomatic carrier, and a 25% likelihood of being unaffected and non-carrier at conception. If one parent is a heterozygous carrier of an HBB pathogenic variant and the other parent has β-thalassemia, each sibling has a 50% chance of inheriting biallelic HBB pathogenic variants and being affected, and a 50% chance of inheriting a single HBB pathogenic variant and being a (typically) asymptomatic carrier.[6] Diabetes mellitus represents a common endocrinopathy linked to transfusional hemosiderosis, affecting 20–30% of adults with β-thalassemia globally and contributing to considerable morbidity. This condition has multiple contributing factors, with iron overload being predominant, making its management particularly challenging. Early intervention, along with closely monitored insulin therapies and enhanced chelation, may improve pancreatic function and help prevent cellular damage.[8] Osteoporosis, marked by low bone density and deterioration of bone microarchitecture, results in increased bone fragility. In individuals with β-thalassemia, osteoporosis is a significant morbidity factor, arising from multiple causes. Ineffective erythropoiesis leads to bone marrow expansion, which reduces trabecular bone tissue and causes cortical thinning. Excessive iron accumulation further contributes by disrupting endocrine function, thereby increasing bone turnover. Additionally, complications from the disease may lead to reduced physical activity, subsequently hindering optimal bone mineralization.

Osteoporosis treatments for individuals with β-thalassemia include bisphosphonates (such as clodronate, pamidronate, and alendronate), which may be used alone or combined with hormone replacement therapy (HRT). Other options include calcitonin, calcium, zinc supplementation, hydroxyurea, and HRT alone to prevent hypogonadism. Denosumab, a fully human monoclonal antibody, works by inhibiting bone resorption and enhancing bone mineral density (BMD). Additionally, strontium ranelate supports bone health by promoting bone formation while inhibiting resorption, leading to a net increase in BMD, greater bone strength, and reduced fracture risk.[9]

Both α- and β-thalassemia carriers (heterozygotes) typically exhibit microcytic hypochromic red blood cell parameters, with or without mild anaemia. The identification of carriers relies on evaluating red cell indices, morphology, and measuring haemoglobin (Hb) fractions. Additionally, iron status should be assessed using ferritin levels, zinc protoporphyrin measurements, and the iron/total iron-binding capacity/saturation index. In β-thalassemia carriers, mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH) are significantly reduced (MCV: 60–70 fl, MCH: 19–23 pg), while α-thalassemia carriers typically show a mild to moderate reduction. The most reliable test for detecting β-thalassemia carriers is the measurement of HbA2, although this can be influenced by the presence of δ-thalassemia.[10]

Due to the complexity of the regulation of the β-globin gene and the role of red cells in many physiological processes, patients can manifest a large spectrum of phenotypes.[4,5] As clinical requirements vary from patient to patient, it is appropriate to emphasize the major differences in the light of potential novel therapeutics. Patients suffering the most severe form, indicated as β-thalassemia major, require chronic blood transfusion for survival. In some cases, splenectomy may be necessary. Currently, bone marrow transplantation is the only definitive cure.[11] Myocardial iron accumulation is a primary contributor to heart failure and early mortality in

patients with transfusion-dependent thalassemia major. Patients experiencing transfusional iron overload are prone to myocardial iron deposition. When myocardial T2 values fall below 10 ms, indicating severe iron overload, there is a markedly elevated risk of heart failure.[12] Monotherapy with deferasirox (DFX) or deferoxamine (DFO) has been shown to significantly reduce total body iron overload, including notable reductions in myocardial iron, in transfusion-dependent thalassemia patients with varying degrees of myocardial iron overload, ranging from mild to severe.[13]

The mechanisms underlying iron accumulation in organs differ between non-transfusion-dependent thalassemia (NTDT) and transfusion-dependent thalassemia (TDT). In NTDT, iron overload is primarily driven by several factors, including enhanced erythropoiesis, hypoxia, and the influence of erythroferrone, which inhibits hepcidin synthesis in the liver.[14]

Unlike NTDT patients, individuals with TDT depend on regular red blood cell (RBC) transfusions for survival. As transfused RBCs age, they are cleared by macrophages in the spleen and liver. However, because there is no natural mechanism for excreting the iron released from these cells, the continuous transfusion of RBCs becomes the main driver of iron overload in TDT patients.[15] The genetic defect in thalassemia results in the production of ineffective red blood cells, which are filtered out by the spleen, causing its enlargement. Splenectomy can increase the lifespan of red blood cells and reduce the frequency of transfusions required.[16] Hematopoietic stem cell transplantation has emerged as a well-established curative treatment for thalassemia major, demonstrating excellent long-term outcomes. However, allogeneic bone marrow transplantation (BMT) is frequently constrained by the availability of suitable donors.[17]

## CONCLUSION

This case sheds light on the evolving challenges in the long-term management of β-thalassemia major, particularly the complex interplay between chronic transfusion therapy, iron overload, and multi-organ complications. The co-occurrence of type 1 diabetes mellitus, osteoporosis, hepatomegaly, and endocrine dysfunction highlights the necessity of early screening protocols and integrated multidisciplinary care. Advances in iron chelation therapy, genetic counselling, and emerging curative approaches such as gene therapy and hematopoietic stem cell transplantation hold promise for improving patient outcomes. This case reinforces the importance of continuous research into optimizing transfusion strategies, mitigating iron toxicity, and developing targeted therapies to enhance the quality of life and prognosis for individuals with β-thalassemia major.

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