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Hypoparathyroidism and Hypothyroidism Secondary to Hemochromatosis in Beta Thalassemia Major

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Abstract

Hemochromatosis, an iron metabolism disorder caused by iron overload, often runs in families. It leads to various issues like cardiomyopathy, liver cirrhosis, and hormonal imbalances. This article presents a unique case of secondary hemochromatosis resulting from repeated transfusions. A 15-year-old boy with severe beta-thalassemia major received about 600 units of packed red blood cells over nine years. This led to clinical hypoparathyroidism and subclinical hypothyroidism, affecting multiple organs. Elevated ferritin and transferrin levels confirmed iron buildup, visible on MRI scans in the liver, pancreas, skeleton, heart, and thyroid gland. Such widespread organ involvement due to transfusion-related hemochromatosis is rare and makes this case noteworthy, especially considering the scarcity of similar reports in Pakistan.

Keywords: hemochromatosis; iron metabolism disorder; cardiomyopathy; liver cirrhosis; hormonal imbalances

Introduction

Excessive iron levels in the body, along with the accumulation of iron in various organs, can lead to a condition known as hemochromatosis. This condition can arise due to genetic factors or secondary causes, resulting in damage to vital organs [1]. One particular genetic mutation impacting the absorption of iron in the intestines gives rise to hereditary hemochromatosis, an autosomal recessive disorder that is more prevalent among Caucasians. Notably, there have been instances documented across different regions globally wherein secondary hemochromatosis was triggered by repeated transfusions. This has been observed in patients undergoing dialysis for end-stage renal disease, as well as those with conditions like aplastic anemia and beta-thalassemia [2]. Interestingly, the impact of repeated transfusions, which lead to an excess of iron in the body, is deemed less detrimental to organ function than hereditary hemochromatosis. This is primarily due to the differing manner in which iron is distributed within the body. In cases of secondary hemochromatosis, iron tends to accumulate within reticuloendothelial cells, as opposed to the parenchymal cells where iron buildup occurs in hereditary hemochromatosis [3].

In the context of this study, we present the case of a patient diagnosed with beta-thalassemia major. Over a span of 9 years, this individual received approximately 600 units of packed red blood cells due to their condition. The patient's hospitalization was prompted by a range of interconnected health issues, including symptomatic hypocalcemia, secondary hemochromatosis, hypoparathyroidism, thyroid irregularities, and mild hepatic abnormalities. This particular case holds significant importance as it sheds light on a unique instance of secondary hemochromatosis, showcasing its manifestation through hypoparathyroidism and hypothyroidism, a presentation that, to the best of our knowledge, has not been widely reported before.

Case Presentation

A 15-year-old boy was admitted to our hospital for the evaluation of symptomatic hypocalcemia. He had been undergoing regular blood transfusions due to

beta-thalassemia major, amounting to approximately 600 units of packed red blood cells. Additionally, he had been taking specialized iron-chelating medication (deferasirox 1,500 mg/day) for the past seven years to manage elevated blood ferritin levels. Despite regular follow-up visits, his hypocalcemia persisted, leading to his outpatient visit to the medical unit for further assessment and treatment.

The patient had no family history of thyroid disease, cervical irradiation, or related conditions. However, his two siblings also had beta thalassemia major. On examination, his temperature was 98.5 °F, pulse rate 92 beats per minute, and respiratory rate 23 breaths per minute. Blood pressure was recorded at 110/70 mmHg. Notably, he exhibited dark skin and slightly pale conjunctiva. His chest examination revealed normal heart sounds, clear breath sounds, and no abnormal findings. Abdominal examination indicated mild tension and slight distention, with the liver palpable about two inches below the right ribcage. No pitting edema was observed in his legs. Neurological assessments revealed positive Chvostek and Trousseau signs.

Laboratory results are summarized in Table 1. Decreased levels of iPTH (parathyroid hormone) and testosterone indicated the involvement of iron deposits in the parathyroid glands and testes, leading to hypoparathyroidism and hypogonadism. Despite treatment with calcium carbonate and alfacalcidol twice a day, 24-hour urine calcium levels (normal range: 100–300 mg/day) had risen to 750 mg/day. Thyroid function tests displayed elevated thyroid-stimulating hormone levels and low free thyroxine levels, confirming secondary hypothyroidism due to iron accumulation. Furthermore, reduced calcium and iPTH levels confirmed hypoparathyroidism resulting from iron deposition in the parathyroid glands.

Table 1: Laboratory Investigations

Test	Reference value	Patient's value
Wbcs (/µl)	4000 - 11000	13000
Hb (g/dl)	11.5 - 17.5	8.7
Platelets (/µl)	150000 - 450000	178000
Bun (mg/dl)	18 – 45	44
Creat (mg/dl)	0.3 - 0.9	0.59
Alt (U/L)	10 – 50	89
Ast (U/L)	8 – 33	75
ALP (U/L)	< 390	357
Total bilirubin (mg/dl)	0.1 – 1	1.4
Na (mmol/L)	135 – 150	131.9
K (mmol/L)	3.5 - 5.1	4.23
Ca (mg/dl)	8 – 10	4.1
Ionised Ca (mg/dl)	4.4 - 5.2	3.1
Ferritin (ng/mL)	24 – 336	> 2000
Transferrin saturation (%)	20 -50 %	81%
iPTH (pg/mL)	15 – 65	1.51
Phosphorus (mg/dl)	3.2 - 6.3	6.03
25 hydoxyVitamin D (ng/mL)	>30	12
Mg (mg/dl)	1.7 -2.55	1.6
Tsh (mIU/L)	0.3 - 4.2	19.7
T_3 (ng/mL)	0.8 – 2	0.523
T_4 (mcg/dL)	5.1 - 14.1	2.17
Testosterone (ng/mL)	2.5 - 8.5	0.025
LDL cholesterol (mg/dl)	<100	54
TAG (mg/dl)	<150	121
RBS (mg/dl)	100 – 125	115
HbA1c (%)	<5.6	5.3

Abbreviations: WBC, white blood cells; Hb, hemoglobin; BUN, blood urea nitrogen; Creat, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; Na, sodium; K, potassium; Ca, calcium; iPTH, intact parathyroid hormone; Tsh, thyroid stimulating hormone; T_3, tri-iodothyronine; T_4, Thyroxin; LDL cholesterol, low density lipoprotein cholesterol; TAG, triacyl glycerol; RBS, random blood sugar; HbA1c, hemoglobinA1c; Mg, magnesium levels

Chest radiography indicated no cardiomegaly. Abdominal and pelvic ultrasonography revealed mild hepatomegaly. Given its heightened sensitivity and specificity for detecting deposits, magnetic resonance imaging (MRI) was preferred over computed tomography (CT). The MRI shown in Figure 1 disclosed diffuse low signals in the liver, pancreas, axial skeleton, thyroid gland, and myocardium sections, indicative of widespread iron overload (Fig. 2). To eliminate the possibility of polyglandular autoimmune (PGA) disorder, the patient underwent evaluations. No symptoms of adrenal insufficiency or oral candidiasis were observed. End-organ function tests (Na, K, BUN, acid/base status) were within normal limits, as serum endocrine autoantibody screening tests were unavailable. This ruled out PGA type 1.

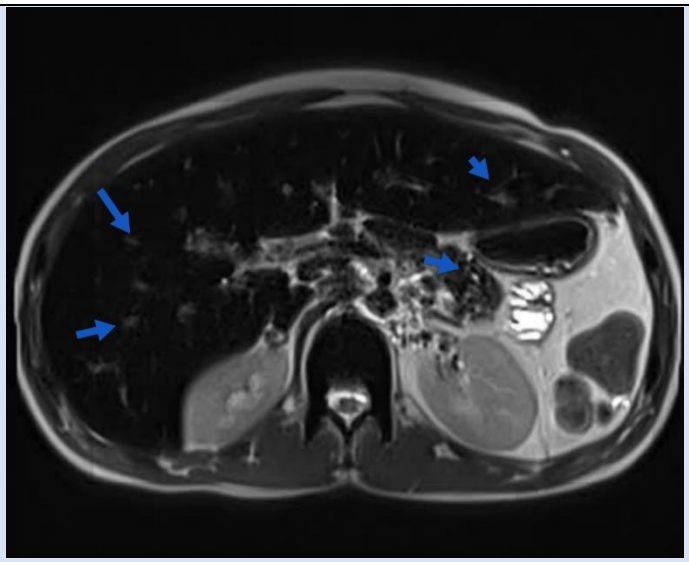

Figure 1: Blue arrows showing iron deposits in the liver and pancreas

To exclude PGA type 2, blood sugar levels and adrenal function were assessed, both yielding normal results. The absence of vitiligo or alopecia, common autoimmune disorder symptoms, was noted. Notably, the patient's blood displayed microcytic characteristics, ruling out PGA type 3, which presents with macrocytic anemia. Treatment ensued, involving increased dosages of calcium and vitamin D supplements following intravenous calcium gluconate administration. Thyroxine was prescribed for hypothyroidism, and a follow-up appointment after two weeks was scheduled. Iron depletion therapy was escalated to address hypogonadism and reduce iron stores.

Discussions

This patient's secondary hemochromatosis stems from excessive iron absorption due to frequent transfusions for beta-thalassemia major. During follow-up monitoring, he was diagnosed with hypocalcemia caused by hypoparathyroidism, subtle hypothyroidism, and liver involvement. The accumulation of iron in various organs due to heightened iron absorption can lead to organ failures, although significant instances of transfusion-induced secondary hemochromatosis are rare [3]. Hemochromatosis, whether genetic or secondary, arises from excess iron in organ tissues, damaging cells and causing organ failure [1]. Patients with hepatomegaly, skin darkening, heart disease, type 2 diabetes, arthritis, and lower urinary tract symptoms can be diagnosed if excess iron or iron infiltration with the HFE genetic mutation is confirmed via tissue biopsy [4].

Normally, the human body maintains iron levels between 3 and 4 g. Daily iron losses are around 1 mg for men and 1.5 mg for menstruating women, balanced by the same amount absorbed by the intestinal mucosa [5]. Conversely, hemochromatosis leads to the absorption of 4 mg of iron daily, raising blood iron and ferritin levels while impregnating organs. Hereditary hemochromatosis, an autosomal recessive trait associated with the HLA-A gene on chromosome 6, accounts for the majority of cases [4]. Secondary causes include excessive iron absorption due to conditions like Mediterranean anemia and sideroblastic anemia, as seen in this study [2]. Repeated transfusions, as in beta thalassemia major or aplastic anemia, can also trigger hemochromatosis.

When macrophages absorb 200–250 mg of iron from a transfused unit of blood, bone marrow abnormalities prevent proper RBC production, leading to iron accumulation in organs and multiple organ failure [3].

Early hemochromatosis symptoms might include arthritis, skin discoloration, fatigue, and weakness. Excessive iron in organs like the pituitary gland, thyroid, parathyroid, liver, heart, and pancreas can result in functional impairment [6]. Liver involvement leads to hepatomegaly, elevated hepatic enzymes, cirrhosis, and hepatocellular cancer. Hemochromatosis patients have elevated mortality risks from conditions like liver cancer, cardiomyopathy, and heart failure, necessitating regular check-ups [7,8]. Diabetes results from liver and pancreatic beta-cell siderosis causing decreased insulin resistance and secretion [6]. Gonadotropin insufficiency can lead to impotence, irregular menstruation, and reduced libido [9]. While less common, siderosis can also impair the thyroid, parathyroid, and adrenal glands [10,11].

Studies on organ damage severity and duration in relation to siderosis are limited. Some studies find associations between blood transfusion quantity and serum ferritin levels, as well as endocrine issues, but more extensive studies are needed to understand these relationships better [12,13]. MRI and CT scans can assess iron impregnation without biopsy. CT is effective for diagnosing hemochromatosis when serum ferritin is over 2,000 ng/mL, and MRI is highly sensitive and specific [14,15,16,17]. In this case, MRI revealed iron overload, confirming secondary hemochromatosis [17]. Patients with transfusion-induced secondary hemochromatosis may experience severe, irreversible functional impairments [13]. Limiting transfusions, using iron-chelating meds as needed, and frequent follow-ups are crucial. Regular screenings and larger studies involving repeated transfusions are required to understand the impact on endocrine failure and other complications.

Conclusions

Individuals with secondary hemochromatosis resulting from recurrent blood transfusions in cases of beta-thalassemia major are at risk of experiencing profound functional limitations, notably disruptions in the endocrine system. Such complications can manifest as enduring issues and significantly impede daily life. Advanced imaging techniques, like MRI scans, have proven valuable in the detection of hemochromatosis-induced hypothyroidism and hypoparathyroidism. Effectively addressing and mitigating these repercussions demands a proactive approach involving regular medical evaluations, scheduled screenings, meticulous transfusion management, and the implementation of iron chelation therapy. To gain a comprehensive understanding of the interplay between transfusion frequency, duration, and the onset of endocrine insufficiencies in secondary hemochromatosis patients, further comprehensive investigations are warranted.

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