Case Report

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Hereditary Hemochromatosis and Alpha-Thalassemia Presenting with Diabetes Mellitus: A Rare Case Report

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Running Title Hereditary Hemochromatosis with Alpha-Thalassemia and Diabetes

ABSTRACT

Hereditary hemochromatosis (HH) is a rare genetic disorder, causing systemic iron overload. High amounts of iron in the bloodstream gradually oversaturate the transferrin which can cause sedimentation of iron in the pancreas, liver, heart, pituitary and joints, though it can establish multiorgan involvements.

We present a case of TFR2 (type 3) HH who had minor α-thalassemia and uncontrolled diabetes mellitus, and discuss the clinical presentation and patient management.

A 33-year-old man with type 3 HH and alpha-thalassemia trait, presented with uncontrolled diabetes mellitus, skin hyperpigmentation and hypogonadism. The patient had high blood glucose ,despite the administration of 80 units of Glargine and 80 units of Aspart insulins per day, but after changing them into human insulins, his diabetes mellitus was surprisingly controlled with only 32 units of NPH and 18 units of Regular insulins. Furthermore, he was treated with testosterone (due to hypogonadism) and Deferasirox (due to iron overload).

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Introduction

Iron is a critical element in the human body. It is not regulated by active excretion, but by the entrance [1]. Hemochromatosis is an iron overload disorder described by Armand Trousseau as “Bronze diabetes” for the first time.

Uncontrolled iron absorption in the intestine leads to high amounts of iron in the bloodstream, though it gradually oversaturates transferrin and makes non-transferrin-bound iron (NTBI). NTBI sediments into the parenchymal cells, especially in the pancreas, liver, heart, pituitary and joints; though it manifests as diabetes mellitus, liver fibrosis and cirrhosis, cardiopathy, central hypogonadism and arthropathy [2-5].

The classic type (type 1) of hereditary hemochromatosis (HH) is caused by mutation of the

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HFE gene, which is the most common type of HH [6]. Non-HFE types include mutation in HJV (type 2a), HAMP (type 2b), TFR2 (type 3) and SLC40A1 (type 4). Transferrin receptor 2 (TFR2) is mostly expressed in the liver and erythroleukemic cells [7]. It acts as an iron controlling factor by sensing the circulating iron and regulates it by hepcidin [8].

Alpha-thalassemia is a hemoglobinopathy in which the alpha chains of hemoglobin are reduced or absent. α-thalassemia intermedia or HbH disease cases may need blood transfusions, which can cause iron overload; but minor α-thalassemia patients are clinically asymptomatic [9]. Some literature reports the coincidence of α-thalassemia and hereditary hemochromatosis [10-12], but it is still a rare condition.

Diabetes mellitus has been seen in 30–60% of patients with HH in different studies; but the type of genetic mutations, ferritin level, or presence of cirrhosis is not predictive for diabetes mellitus development. In the majority of patients, insulin requirements or blood glucose level is not influenced by iron depletion [13].

In this report, we present a case of TFR2 (type 3) HH who had minor α-thalassemia and was admitted for uncontrolled diabetes mellitus.

Case presentation

A 33-year-old man was admitted to the Endocrinology Department of University Hospital complaining of uncontrolled diabetes mellitus (DM). He was a known case of DM in the last 3 years, being treated with 25 units of Glargine insulin daily and 20 units of Aspart insulin three times a day; however, his blood glucose was uncontrolled. He had lost about 10 kilograms in the last 6 months, complaining of weakness, bone pain and decreased libido. In physical examination, he was conscious and had normal vital signs. His skin showed hyperpigmentation (Fig. 1). Other examinations did not have any remarkable points. Complete blood count revealed a mild microcytic and hypochromic anemia, the iron profile was impaired, and hypothalamic-pituitary axis investigations showed central hypogonadism (Testosterone = 0.6 ng/mL, LH = 1.8 IU/L, FSH = 1.2 IU/L), the anti-GAD antibody was negative, and there was a decreased c-peptide level (0.08 ng/mL). Hepatic laboratory findings include PT, INR, and albumin were normal, but liver enzymes were raised. Some of the other laboratory investigations are shown in Table 1.

Abdominal ultrasonography revealed mild hepatosplenomegaly and grade I fatty liver; but unfortunately, liver MRI was not possible to do in our center.

Cardiac investigations, consist of electrocardiography and echocardiography were normal (EF = 50-55% and PAP = 20 mmHg).

We did a genetic study and based on the clinical and laboratory findings of that study, a homozygote mutation of AVAQ 594-597 del in the TFR2 gene confirms the diagnosis of hereditary hemochromatosis. Considering the diagnosis, the patient's anemia could not be

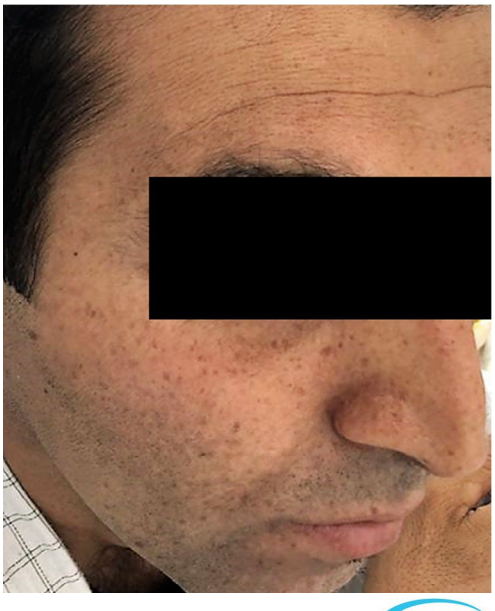

Fig. 1. Hyperpigmented skin

Table 1. Laboratory investigations

Biochemical parameter	Value
Fasting blood sugar (mg/dl)	410
HbA1C (%)	11.5
Hemoglobin (g/dl)	10.7
Platelet count (cu mm)	140,000
Serum cortisol(µg/dL)	18
ACTH (ng/mL)	75
FreeT4 (ng/dL)	1.2
TSH (mIU /L)	2.5
SGOT (U/L)	161
SGPT (U/L)	174
Serum alkaline phosphatase (U/L)	251
Serum Ca (mg/dL)	9.9
PTH (ng/L)	40
Serum iron (µg/dl)	224
TIBC (µg/dl)	326
Serum ferritin (ng/dl)	3544
Prothrombin time (control) (s)	13.4

ACTH: Adrenocorticotropin hormone; PTH: Parathyroid hormone; TIBC: Total iron-binding capacity

explained. Therefore, hemoglobin electrophoresis was done, showing alpha-thalassemia, which is not so probable in companion with hemochromatosis.

Due to anemia, he could not go under phlebotomy, therefore; we started Deferasirox 500 mg BID for his high ferritin level. Furthermore, according to hypogonadism, testosterone was prescribed and the dose of insulin was increased after the admission, although the blood sugar could not be controlled with 80 units of Glargine insulin daily and 80 units of Aspart insulin divided into three doses per day. Hence, we decided to change it to human insulin because of the high cost of insulin analogs, and surprisingly his blood glucose was controlled with only 32 units of NPH insulin divided into two doses per day and 18 units of regular insulin divided into three doses a day. Finally, after 3 months, DM was relatively controlled (FBS = 139 mg/dL and HbA_{1C} = 7.1% after 3 months) and ferritin level decreased (500 ng/mL).

Discussion

In this report, we present a case of hereditary hemochromatosis with a trait of alpha thalassemia, who had poorly controlled diabetes mellitus with recombinant analog insulins (Glargine and Aspart), replying to human insulins (NPH and regular). Hereditary hemochromatosis is a rare genetic disorder presented in 5 types (based on the mutated gene). Type 1, 2A, 2B, and 3 are all about the hepcidin loss of function, but type 4 is caused by a gain-of-function mutation resulting in resistance to hepcidin [14]. All of these types cause systemic iron overload and present with the same signs and symptoms in different severity and age of onset. These manifestations include skin pigmentation, liver fibrosis and cirrhosis, endocrine disorders such as diabetes mellitus, hypothyroidism, or hypogonadism, cardiomyopathy especially in young adults, and some non-specific manifestations such as fatigue, mild hypertransaminasemia and arthralgia [14, 8, 15]. Our patient was a case of type 3 hereditary hemochromatosis, which is due to a mutation in the TFR2 gene, with a 0.0001 to 0.0004 prevalence; causing lower expression of hepcidin resulting in increased enteric iron absorption [6, 16].

The standard treatment for HH is phlebotomy. Phlebotomy lessens the total iron storage of the body and also reduces the amount of iron in the tissues. Therefore, signs and symptoms such as fatigue, skin pigmentation, raised liver enzymes, abnormal cardiac function, and even high blood glucose can be alleviated by regular phlebotomy [17]. But the important factor is the level of serum hemoglobin. Our patient had mild anemia due to alpha-thalassemia, so the best treatment was iron chelation, as the second line of treatment. We administered Deferasirox 500 mg BID which controlled his ferritin level properly.

Insulin deficiency and β-cell damage, as the main mechanisms for the development of diabetes in these patients, and insulin resistance due to hepatic damage are involved in the pathogenesis of diabetes in HH. Phlebotomy may prevent the progression of diabetes if started immediately, although the majority of patients will experience no significant change or worsening in their glucose metabolism control [18, 19]. It seems that in our patient both of these mechanisms are responsible for diabetes and he experienced better diabetes control after modification of insulin therapy and prescription of Deferasirox.

Ethical Considerations

Consent

The consent was taken from the patient for the case report to be published.

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed in preparing this article.

Conflict of interest

Authors declare that there is no conflict of interest.

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