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Hemochromatosis Presenting with Diabetic Ketoacidosis: A Rare Case Report

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CASE REPORT

ABSTRACT

Hemochromatosis, although increasingly recognized by clinicians, is still underdiagnosed because it is often considered a rare disorder. The fully established disease consists of cirrhosis, diabetes, and skin pigmentation (bronze diabetes). Diabetes can occur as a result of direct islet cell damage due to iron infiltration. Presentation with diabetic ketoacidosis is rare, and only few cases have been reported. This case report is of a patient with hemochromatosis presenting with diabetic ketoacidosis.

Keywords: Hemochromatosis, diabetic ketoacidosis, hypogonadism, cirrhosis, phlebotomy

INTRODUCTION

Hemochromatosis is a multisystem disease with excess iron deposition in several organs such as the liver, heart, pancreas, joints, skin, and endocrine system that damages these structures and causes clinical manifestations like cirrhosis, heart failure, diabetes mellitus, arthralgias, skin hyperpigmentation, and hypogonadism (1). Primary hemochromatosis is an autosomal recessive condition caused by an abnormal HFE gene, whose protein product regulates iron absorption from the gastrointestinal tract. Secondary hemochromatosis (non-reticuloendothelial system iron deposition) is rare and is usually seen in association with diseases that chiefly cause hemosiderosis. Hereditary hemochromatosis (HH) remains the most commonly identified genetic disorder among Caucasians. Although its geographic distribution is worldwide, it is seen most commonly in populations of northern European origin with a prevalence of approximately 1 per 220–250 individuals (2). Primary iron overload is uncommonly encountered among Indians. Two missense mutations (C282Y and H63D) have been described in the HFE gene that encodes a protein, which is highly similar to HLA class 1 molecules in patients suffering from HH on the basis of phenotypic data.

Diabetes mellitus can be seen in 30–60% of patients with HH; therefore, polyuria, polydipsia, and high blood and urine glucose levels may be found. The type of mutations for HH, ferritin level, or cirrhosis presence is not predictive for diabetes mellitus development. In majority of patients, insulin requirements or glucose level is not influenced by iron depletion (3). Although diabetes mellitus is common, diabetic ketoacidosis as a manifestation of HH has rarely been described. Here we report the case of a patient with hemochromatosis presenting in diabetic ketoacidosis.

CASE REPORT

A 35 year old nonalcoholic vegetarian female was presented to the emergency department with vomiting and altered sensorium over the last 24 hours. Vomiting was non-bilious, non-projectile, and contained partially digested food particles. The patient had been diagnosed with diabetes one year ago, for which she was not taking any treatment. She was married for 5 years and had never been pregnant. There was no history of fever, joint pains, seizure, burning micturition, urinary incontinence, or bowel incontinence. Her family history was not significant. There was no past history of any blood transfusions, tuberculosis, asthma, hypertension, high-risk sexual behavior, or intravenous drug abuse. The patient's age at menarche was 13 years with a regular menstrual cycle of 28 days, lasting for 2 to 3 days with normal blood flow, but she was now experiencing amenorrhea over the last 4 years.

On examination, the patient was drowsy, disoriented, and had diffuse hyperpigmentation. She was severely dehydrated with dry mucous membranes and delayed skin turgor. Neck rigidity was absent. The respiratory rate was 34/min with a blood pressure of 100/70 mm of Hg. The pulse rate was 120/min regular, low volume. Pallor was present but there was no evidence of icterus, cyanosis, clubbing, or lymphadenopathy. Neck veins were collapsed. Her breath had a fruity odor. Breast and pubic hair were tanner stage 5. Neurological examination was unremark-

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able. Abdomen examination revealed hepatosplenomegaly but no evidence of shifting dullness or fluid thrill. There were no stigmata indicating chronic liver failure.

On investigation, the patient had pancytopenia with Hb 9 gm%, TLC 3200/mm^3, and a platelet count of 80000/mm^3. Her blood sugar level was 440 mg/dL. Arterial blood gas showed anion gap metabolic acidosis with a pH of 7.12, bicarbonate 10 meq/L, and a raised serum anion gap. Urine was positive for ketone bodies. Serum sodium, potassium, and lactate were normal. She was treated for diabetic ketoacidosis with IV fluids and insulin infusion following which she gradually regained consciousness. On further investigation, serum transaminases were raised with SGOT 350 U/L and SGPT 300 U/L. Tests for viral markers and autoimmune serology were negative. Serum electrophoresis, levels of alpha 1-antitrypsin, and ceruloplasmin were normal. However, iron studies were markedly abnormal with a raised transferrin saturation of 70.6% (30–50%) and serum ferritin of 1357.16 ng/mL (29–248 ng/mL). On USG, abdomen minimal free fluid was present, liver was enlarged measuring 18 cm with altered echotexture, spleen size was 15 cm, and portal vein diameter was 14 mm suggesting portal hypertension. Upper GI endoscopy showed low-grade esophageal varices. Patient was further investigated for secondary amenorrhea. Urine pregnancy test was negative. Serum FSH (0.5 IU/L), LH (0.5 U/L), and estradiol levels (55 pmol/L) were low revealing hypogonadotropic hypogonadism. Free T3, T4, and TSH were normal with values of 5 pmol/L, 12 pmol/L, and 3.8 mIU/L, respectively. The serum prolactin level was normal. Chest radiograph and ECG were normal. MRI brain showed heterogeneous low signal intensity over the anterior lobe of the pituitary gland. In view of skin hyperpigmentation, diabetes mellitus with compensated cirrhosis and investigations showing pancytopenia, raised transaminases, transferrin saturation and ferritin levels. With a presumptive diagnosis of hemochromatosis, a liver biopsy was performed. The liver biopsy findings were consistent with changes of early cirrhosis (Figure 1). Perl's Prussian blue staining showed grade 3 iron deposition in parenchymal cells consistent with a diagnosis of hemochromatosis (Figure 2). Results of the genetic testing revealed the patient to be homozygous for the mutation H63D. Patient improved with insulin therapy and was treated with periodic sessions of phlebotomy. However, she was not willing to partake in continued therapy and did return up for further sessions. Informed consent has been taken from patient for publication of the case report.

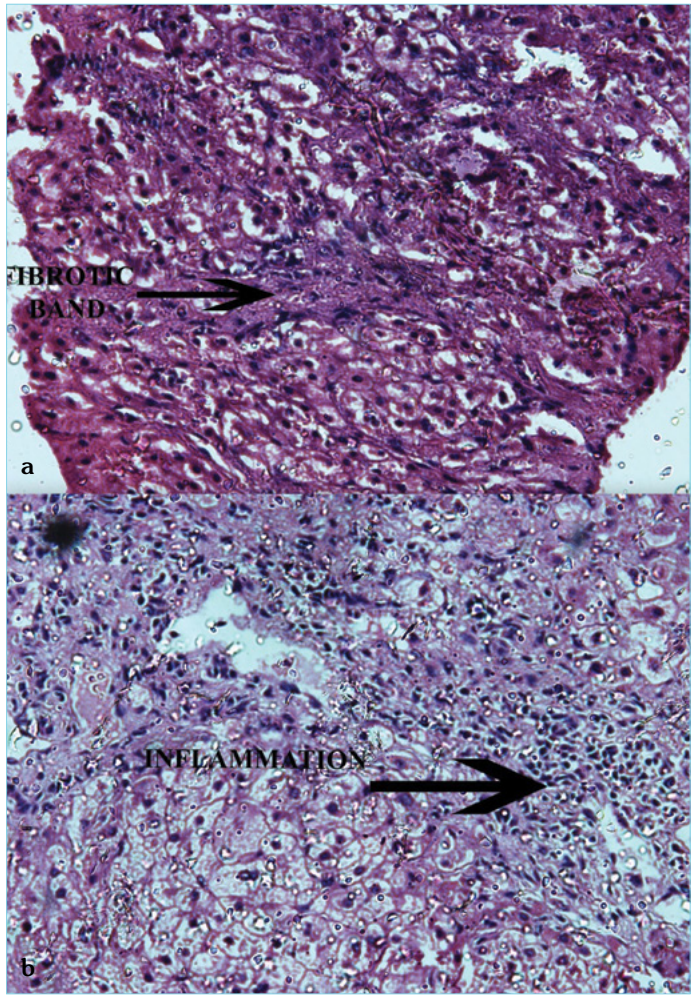

Figure 1. H&E staining of liver tissue showing cirrhosis and fibrotic bands (a), H&E staining of liver tissue showing inflammation and hepatocyte degeneration (b)
H&E: Hemotoxylin and Eosin

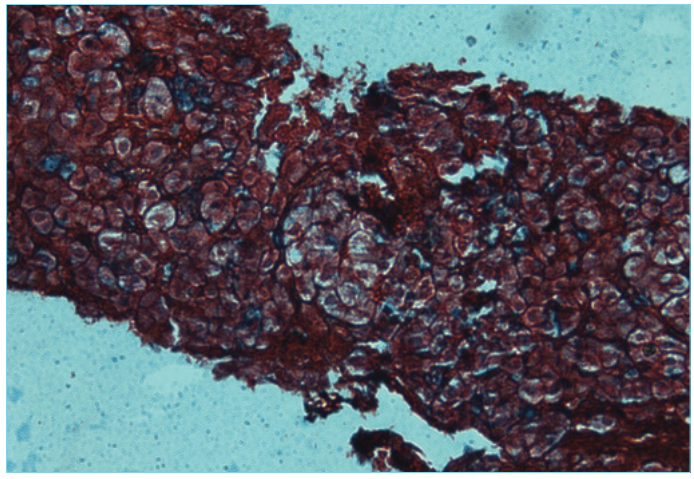

Figure 2. Perls' Prussian blue staining showing grade 3 iron stores

DISCUSSION

Hemochromatosis is an iron overload disorder that can be primary or secondary. Primary hemochromatosis is an autosomal recessive disease from dysregulation of iron absorption due to a mutation on HFE gene located on chromosome 6 (4). Secondary hemochromatosis occurs in diseases of ineffective erythropoiesis like thalassemia. There is an increase in intestinal absorption of iron leading to a state of iron overload in multiple organs, thus leading to a clinical spectrum ranging from diabetes mellitus, cirrhosis, hypogonadism, infertility, cardiomyopathy, to arthralgia (5). Barring early clinical symptoms like weakness, fatigue, and abdominal discomfort, these manifestations appear later in life when the total body iron content has reached greater than 20 g, more than 5 times the normal limit. Such a degree of accumulation occurs over a period of 10–20 years and the disease presents most commonly in middle age (6, 7). Diabetes mellitus, liver disease, or skin hyperpigmentation develops in about half of HH cases (8).

Diabetes in hemochromatosis results from insulin resistance and decreased insulin secretion from the pancreas. The degree of glucose intolerance depends on the stage of iron deposition and stage of liver disease (9). Early disease is associated with insulin resistance that partially improves with phlebotomy. When advanced iron load occurs, iron accumulates in beta cells, deteriorates pancreatic insulin secretion, and leads to insulin dependent diabetes, which cannot be recovered with iron removal. The appearance of diabetes of this severity, similar to diabetic ketoacidosis, is distinctly unusual. Only few case reports of diabetic ketoacidosis as a manifestation of HH have been reported in the literature (9, 10). The relative ease with which a patient's diabetic ketoacidosis was controlled points towards insulin resistance along with insulin deficiency in our patient.

Hypogonadism can antedate other presentations of hemochromatosis. The presentations are decreased libido, infertility, impotence, and amenorrhea. It occurs in both sexes due to decreased gonadotropin secretion from pituitary glands because of iron-induced cellular damage (11).

Phlebotomy is the cornerstone of therapy for hemochromatosis. Different organ involvements may respond variably to therapy. In a study conducted on 2,851 hemochromatosis patients to assess the symptoms and the response to therapeutic phlebotomy, it was found that 86% of patients reported symptom improvement with phlebotomy. More than half of the respondents reported improvement in skin bronzing and extreme fatigue (58.8% and 54.4%, respectively). Depression (40.8%), abdominal pain (22.3%), impotence or loss of libido (12.7%), joint pain (9.2%), and cardiac failure (6.2%) also showed improvement. Liver function tests and hepatic fibrosis also improved after phlebotomy (12).

CONCLUSION

Early diagnosis is essential, and the combination of symptoms, when they are all present, is suggestive of hemochromatosis; however, the diagnosis is not always easy to infer clinically in young subjects. To conclude, hemochromatosis should be kept as a differential in patients presenting with a constellation of conditions such as cirrhosis, hypogonadism, and diabetes.

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Peer-review: Externally peer-reviewed.

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