Primary Hemochromatosis Presenting as Type 2 Diabetes Mellitus: A Case Report with Review of Literature

Abstract

Hemochromatosis is an autosomal recessive genetic disorder resulting in increased intestinal absorption of iron and eventually to iron overload. The onset of symptoms is usually seen around 40 years of age. Iron overload causes tissue damage in liver, pancreas, skin, joints, heart, and gonads. Approximately 50% of patients diagnosed with hemochromatosis will have either type 1 or type 2 diabetes mellitus (DM) because of selective beta-cell damage due to iron overload and leads to impaired insulin synthesis, release, and insulin resistance. Early diagnosis and treatment of hemochromatosis prevents the development of diabetes. We present a case in a 48-year-old male with a history of DM for 6 months and skin pigmentation over face for 1 year.

Keywords: *Diabetes mellitus, iron metabolism, liver, primary hemochromatosis*

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Introduction

Primary/hereditary hemochromatosis (PH) is the most common genetic disorder of Caucasians characterized by iron overload syndrome with enhanced intestinal absorption of iron associated with potential iron overload in peripheral tissues presenting with complications as cirrhosis, hepatocellular carcinoma, diabetes mellitus (DM), and heart diseases.[1-5] It is the most common single gene disorder in the US native population. The effects of genetic mutations are triggered by acquired and environmental factors.[6,7]

PH is caused by mutation of HFE or non-HFE genes.[8] Secondary hemochromatosis is due to alcohol use, excessive iron and vitamin C intake, oral contraceptives, and blood transfusions.[3]

Very few cases of PH have been reported in India.[9,10]

Case Report

A 48-year-old male presented with generalized weakness, easy fatigability, pain in extremities, loss of weight, and loss of concentration/interest in routine work for 6 months. He had increased skin pigmentation, especially over the face for 1 year which he considered it as sunburn [Figure 1]. He was a known case of type 2 DM on medication for 6 months. No history of blood transfusion or jaundice noted. The patient was a chronic alcoholic since 25 years. Family history was insignificant. Physical examination revealed anemia, bald tongue, pallor, hepatomegaly, and splenomegaly. Endoscopy showed grade II esophageal varices. A provisional clinical diagnosis of type 2 DM with cirrhosis of liver and probably with hemochromatosis was offered.

Significant laboratory investigations are shown in Table 1. Ultrasound and magnetic resonance imaging showed hepatomegaly with nodular margin, hypertrophied caudate lobe, and hypointensity suggesting cirrhosis of liver associated with hemochromatosis. Spleen was enlarged with hypoechoic areas. Mild ascites was present. The liver biopsy microscopically showed 5–6 portal triads having features of bile duct proliferation with mild–to-moderate fibrosis extending into hepatic lobules forming incomplete bridging fibrosis. The portal triad showed intra- and extra-cellular deposits of golden yellow colored pigments. The hepatocytes especially in periportal areas showed similar pigment deposits. Perl's stain showed increased iron deposits [Figure 2a and b]. Histopathological features were consistent with hemochromatosis. A final diagnosis of PH with type 2 DM and cirrhosis was made. The patient was lost for follow-up.

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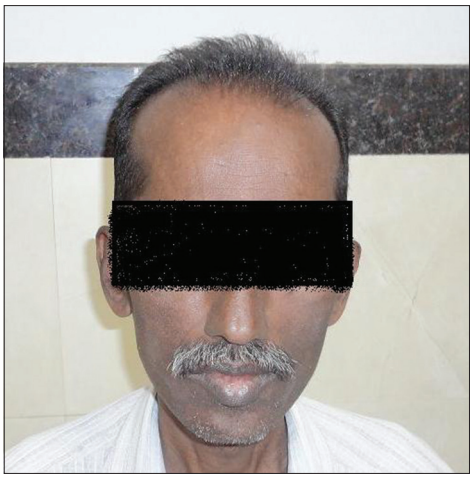

Figure 1: Photograph of the patient showing skin hyperpigmentation in the face

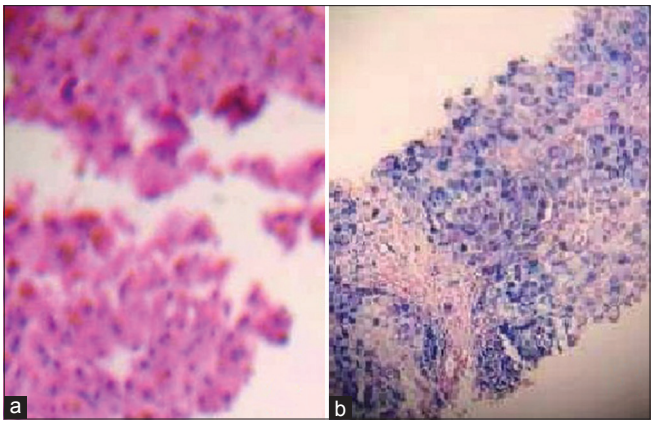

Figure 2: (a) Microphotograph showing features of cirrhosis and pigment deposition in liver biopsy (H and E, ×100). (b) Microphotograph showing iron deposition in liver biopsy (Perl's, ×100)

Discussion

Hemochromatosis was first described by Trousseau (1889) as a triad of glycosuria, cirrhosis, and hyperpigmentation of skin. The term "Hemochromatosis" was first used by Von Recklinghausen (1889). The close association between PH and HLA-A3 was first described by Simon *et al* (1977).[2,3,9] HFE gene defect was first described in 1996 in relation to PH.[9]

PH is commonly seen in Caucasians population of Northern European origin, especially Nordic or Celtic ancestry with the prevalence of approximately 1 per 220–250 individuals.[1,2] With high frequency of consanguineous marriages in many Asian populations and complete penetrance of non-HFE gene, PH prevalence may be more in Asians than previously thought especially those migrated to developed countries and exposed to the western diet.[10]

The first case in India was reported in a female with porphyrins in urine and unusual findings on compound tomography of kidney in the year 2000. Very few cases of PH have been reported in India and reports of genetic study is rare.[9] Genetic mutations and environmental factors regulate iron absorption that modulate disease manifestation in Indian populations.[9,10] In our case, the patient was a chronic alcoholic with no significant family history, genetic analysis was not done.

PH seldom manifests before the age of 40 years as it takes years to build up enough iron to cause tissue damage.[6,8] Males present with PH 4–10 times more compared to females and women present approximately 10 years later. More men than women have increased ferritin levels. This is due to menstrual blood loss and maternal iron loss during pregnancy having a protective effect for women. However, in a study where patients were identified by screening studies, the age of diagnosis and the number of men and women were equal.[7,9] In the present case, the patient was a male of 48 years old.

Table 1: Significant laboratory investigations of the present case

Biochemical parameters	Values
Fasting blood sugar (mg/dl)	252
Postprandial blood sugar (mg/dl)	334
Total bilirubin (mg/dl)	0.9
Direct bilirubin (mg/dl)	0.4
Serum albumin (g/dl)	2.8
Serum globulin (g/dl)	4.4
Albumin: globulin ratio	0.6
SGOT (U/L)	95
SGPT (U/L)	82
Serum alkaline phosphatase (U/L)	251
GGT (U/L)	14
Serum iron (µg/dl)	252
Serum ferritin (ng/dl)	>1500
Transferrin saturation (%)	101.1
Platelet count (cu mm)	79,000
Prothrombin time (control) (s)	15.4 (13.1)
Activated partial thromboplastin time (control) (s)	46.8 (25.2)

GGT: Gamma-glutamyl transferase; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase

Iron overload occurs in organs such as liver, pancreas, skin, heart, and brain and gives rise to cirrhosis, diabetes, and cardiomyopathy.[9] In the present case, iron overload was manifested in liver, pancreas, and skin.

Hemochromatosis patients develop diabetes mellitus. The factors which contribute to the pathogenesis are beta cell damage, insulin resistance, and underlying genetic tendencies. The selective beta cell damage is due to iron overload giving rise to impaired insulin synthesis and release. Iron in PH is deposited in parenchymal cells of organs and not in the reticuloendothelial cells. Alfa cell function is not impaired. Insulin resistance is due to marked liver fibrosis by which patient require large amount of insulin. Family history of diabetes is reported in 25% of patients with hemochromatosis.[8] In the present case,

the patient presented with type 2 DM with no significant family history.

Hemochromatosis is associated with porphyria cutanea tarda (PCT) because of iron load which affect quantity and activity of uroporphyrinogen decarboxylase by which uroporphyrinogen accumulates in the skin and present as blisters. In addition, iron interferes with heme synthesis pathway.[3] Recently, HFE hetero- and homo-zygosity has also been linked to nonhepatocellular malignancies including female/male breast cancer and prostate cancer.[9]

In many cases, routine investigations showed abnormal iron studies (by family screening), but approximately 75% of them did not present with symptoms/signs. The frank clinical manifestation in fully established disease depends on organ involved, i.e., liver (cirrhosis, extrahepatic manifestation of liver disease), pancreas (diabetes mellitus), skin (hyperpigmentation), joints (arthralgia of second and third metacarpophalangeal joints, arthritis, and chondrocalcinosis), heart (arrhythmias, cardiomyopathy, and heart failure), and gonads (hypogonadism, testicular atrophy, and impotence, libido).[1,3,4,7-9]

The other constitutional symptoms are fatigue, weakness, weight loss, apathy, pain in arms/legs, muscle tenderness, and cramps in legs. In early years, hyperpigmentation of skin resembles sunburn, and it forms the triad of bronze diabetes.[1,9] Liver is the most frequent organ affected.[8] PCT has presented as the first sign of underlying hemochromatosis.[3] PH associated with hypogonadotropic hypogonadism and decreased Leydig cell reserve is reported in 1992.[9] About 50% cases diagnosed with hemochromatosis will have type 1 or 2 diabetes. The likelihood of hemochromatosis in the adult population of diabetic patients is reportedly between 1% and 2%. Sometimes, diabetes is the only apparent manifestation of hemochromatosis in unrecognized cases.[8] McClatchie *et al*. and Jones described the association of PH with infections, is due to alteration in iron-dependent host-pathogen interaction. Three cases of multiple liver abscesses in patients due to *Yersinia enterocolitica* which is an iron-dependent bacterium that relies entirely on exogenous iron are reported. With liver abscess, long-term follow-up for increased iron stores is recommended for diagnosis of hemochromatosis in asymptomatic patients.[2,4] In this case, the patient first presented with skin pigmentation which was neglected as sunburn. Six months later, the patient presented with DM, cirrhosis, and iron overload.

The diagnosis of hemochromatosis can be done by biochemical, radiological, histopathological, and genetic investigations correlating with clinical manifestations and family history.[9] Serum ferritin levels are a predictor of advanced fibrosis and cirrhosis in confirmed cases.[1] Liver biopsy was the gold standard for the diagnosis to know increased iron stores and early periportal fibrosis.[8,9] However, the liver biopsy has become less important after advent of genetic analysis. Liver biopsy is stained with Perl's stain and hepatic iron content is estimated by quantitative and semi-quantitative methods. Hepatic iron index of more than 0.9 μmol/g/year with abnormal liver tests suggests diagnosis of PH. Genetic testing was started in late 1990 which confirm the diagnosis of PH. The genetic testing helps in HFE-related PH asymptomatic probands and presymptomatic relatives of the patients.[1] In the present case, the diagnosis was done by radiological, biochemical, and histopathological findings.

Phlebotomy is done with target level of serum ferritin level of 50–100 μg/L.[1] Extensive liver damage give rise to cirrhosis which is a high risk for HCC than in noncirrhotic. Hence, regular therapeutic venesection is recommended as preventive therapy. The cause of death in PH is HCC in 30% cases and complications of cirrhosis in 20% cases.[1] In the present case, phlebotomy was not done.

Screening is recommended to first degree relatives by both genotype and phenotype (iron studies) analysis for early diagnosis and prevent complication.[1] Screening diabetic patients for hemochromatosis is currently debated. Genetic screening of general population is more complicated with questionable practicability and acceptability.[8,9] In the present case, the first degree relatives were asymptomatic and genetic screening was not done.

Conclusion

Isolated cases of PH are diagnosed in Indian population. Hence, clinicians should be aware that hemochromatosis occurs in an Asian population with variable iron overload and should be recognized/diagnosed early for prompt therapy and prevent complication/premature death.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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