Clinical Conference :

DIABETES MELLITUS AND HYPERPIGMENTATION IN AN ADULT PRESENTING WITH GAGHEXIA AND UNGONGIOUSNESS

Sood A

Fifty year old woman was admitted to the hospital with diabetes mellitus, weight loss and generalized hyperpigmentation.

The patient was detected to be diabetic 3 years ago, when she complained of generalized weakness, loss of weight and polyuria. She was unsuccessfully treated with sulfonylurea for one year initially and then insulin injections were started. At present she was taking 46 units of insulin per day in divided doses, but control of her blood sugars was poor. The patient had not received any insulin two days before the admission. There had been four episodes of hypoglycemia in last one year. There was no history of diabetic ketoacidosis in the past. There was considerable weight loss over last 4 years. Her breasts had atrophied. There was disappearance of axillary and pubic hair.

8-10 days prior to admission, the patient complained of increasing generalized weakness, anorexia and decreased oral intake. One week before admission, she started developing progressive drowsiness. She developed watery diarrhoea, occuring approximately 2-3 times per day, three days before admission. The diarrhoea was associated with vomiting. There was no abdominal pain. One day before admission, the patient became unconcious.

There was no history of salt craving, postural hypotension or significant muscle cramps. The patient never had icterus or pedal edema. There was a history of cough with scanty mucopurulent expectoration. There was no significant family history and no history of alcohol intake. The patient was not married. She was menopausal for last two years. Previous menstrual history was normal. There was no past history of tuberculosis.

On examination, the patient was unconcious, responding slightly to deep painful stimuli. She was emaciated dehydrated with generalized hyperpigmentation and mild alopecia. There was no pallor, icterus or cyanosis. Glossitis was present. No significant lymphadenopathy was present. Jugular venous pressure was normal. Pulse was 90/min, reg, west and normal in character. Blood pressure on admission was 60 mm Hg. The skin was thin, atrophic and hyperpigmented. Mucosa was normal. No axillary or pubic hair were present. Mild pedal edema was present. The patient had decreased air entry with dullness on percussion on the right infrascapular region with coarse crepitations in right inframammary, infra-axillary and infrascapular region Gr II/VI ejection systolic murmer was present in left parasternal area. Abdomen on palpation was tense with mild diffuse tender-

Department of Endocrinology & Metabolism, All India Institute of Medical Sciences, New Delhi - 110 029.

ness. Liver was palpable 3 cm, firm, mildly tender. There was no splenomegaly. Shifting dullness was present. Deep tendon reflexes were sluggish. No focal neurological deficit was present.

Urine sugar was+ + + + and urine was positive for acetone. There was no proteinuria. Microscopic examination of urine was normal. Blood glucose was 342 mg/dL blood urea 27 mg/dL, serum creatinine 0-4 mg/dL, sodium 127 mEq/L, potassium 5.0 mEq/L, Blood hemoglobin was 12.7 gm/dL, hematocrit 46%, total leukocyte count 5,500, with 71% polymorphs, 22% lymphocytes, 2% eosinophils and 1% basophils, platlets $2xl0^5$/cumm, erythrocyte sedimentation rate 60 mm fall in 1st hr, serum iron 160 ug/dL, transfer in saturation 80%, total iron binding capacity (TIBC) 200 ug/dL, unsaturated iron binding capacity (UIBC) 40 ug/dL, serum feritin 5580 ng/mL. Peripheral blood smear was normal. Serum bilirubin was 0.5 mg/dL, serum aspartate aminotransferase (SGOT) 30 K.U., serum alkaline aminotransferase (SGPT) 55 K.U., serum alkaline phosphatase 51 K.A., units, serum albumin 3.2 mg/dL, serum globulin 3.0 mg/dL, serum calcium 9.0 mg/dL, serum phosphate 3.9 mg/dL, serum amylase 178 Somogyi units, prothrombin time 13 sees (control 13 sees).

ECG showed T wave flattening in lead III, a VF, and inverted T waves in V_1 to V_4. Serum HBs Ag was negative. Chest x-ray revealed bilateral parenchymal infiltrates and right sided pleural effusion. Plain X-ray abdomen was normal. Abdominal ultrasound showed mild ascites with hepatomegaly. No adrenal mass was seen. Barium enema study was normal, 24 hrs urinary albumin was 60 mg, creatinine 120 mg, sodium 9 mEq, calcium 145 mg, inorganic phosphorus 312 mg. Urine culture was sterile. Ascitic fluid was straw coloured, with protein 0.7 gm/dL, full of red blood cells, 500 leukocytes (mostly neutrophils), few reactive mesothelial and inflammatory cells; culture was sterile; AFB smear and culture was also negative. Vaginal smear showed atrophic cells. X-rays of the skull and sella were normal CT of the head showed mild cerebral atrophy. CT of the abdomen demonstrated increased attenuation value of liver (90 Hounsified units, H.U.) compared to spleen and kidneys (50 H.U. and 30 H.U. respectively); pancreas showed fatty infiltration and the kidneys showed small areas of increased attenuation in calyceal region. Islet cell antibodies in the serum were absent. Plasma cortisol at admission was > 50 ug/dL Prolonged ACTH stimulation test done later was normal. Basal LH and FSH were 1.25 I.U/L and 1.01 LU./L, and plasma estradiol was undetectable. Basal prolactin was 135 I.U./L, and did not pick up by 100% on TRH stimulation. The patient was given rapid intravenous fluids with insulin injections. Injectable steroids were started. The sensorium of the patient improved gradually. Blood pressure, became 100/60 mm Hg, with no postural fall. A biopsy was performed to confirm the diagnosis.

Clinical Discussion

This patient who was detected to be diabetic for three years, had presented with diabetic ketoacidosis. The precipitating case of diabetic ketoacidosis seems to be an acute episode of gastroenteritis and stopping of insulin injections. In addition the patient seems to have pulmonary tuberculosis as evidenced by the findings of chest X-ray.

The presence of hypotension could be due to fluid loss because of diarrhoea and vomiting associated with poor oral intake. On the other hand, hypotension occuring in a patient with generalised hyperpigmentation and considerable weight loss may be due to Addisonian crisis, and steroids were probably started with this in mind. Presence of pulmonary tuberculosis tends to support such a diagnosis as dissemination of tuberculosis to adrenals might be responsible for Addisonian crisis. The patient had 4 episodes of hypoglycemia in last one year; frequent hypoglycemic episodes may occur in Addisonian's disease. The stress of acute illness and diabetic ketoacidosis may be responsible for precipitating the crisis. But the value of plasma cortisol at admission being > 50 ug/dL and prolonged ACTH stimulation test being normal, strongly militates against the diagnosis of Addisonian crisis. Also, there was no history of salt craving or muscle cramps.

The presence of hyperpigmentation in a patient with diabetes, should alert one to the possibility of hemochromatosis. Values of serum iron, transferrin saturation, total iron binding capacity (TBIC), unsaturated iron binding capacity (UIBC) and serum ferritin support the diagnosis of idiopathic hemochromatosis. However one must rule out other causes of iron overload[1.2].

Primary chronic liver disease may lead to secondary deposition of iron in the liver, associated with increase in serum iron and serum ferritin. This occurs more commonly in patients with history of excessive alcohol intake. It is probably due to hyperabsorption of iron in the intestine. Inspite of increased serum iron and ferritin, the total body iron stores are not markedly increased. The basis on which such patients can be distinguished from idiopathic hemochromatosis is : (i) Quantitative estimation of iron in liver biopsy specimen, the value of which is far greater in idiopathic hemochromatosis than in chronic liver disease. Also, patients with primary liver disease do not have clinical evidence of systemic iron overload, (ii) demonstration of iron overload in the family of the patient, especially associated with HLA-A3 haplotype. Presence of HLA-A3 haplotype in itself favours the diagnosis of idiopathic hemochromatosis. (iii) Total iron binding capacity (TIBC) is decreased in idiopathic hemochromatosis, where as there may be no change in the case of chronic liver disease. Serum ferritin, which otherwise is a reliable indicator of total body iron store, may be increased out of proportion to iron stores in the presence of hepatocellular necrosis. Finally, when patients with primary liver disease are subjected to phlebotomy, they develop iron deficiency anemia quite rapidly, unlike ideopathic hemochromatosis who can tolerate number of phlebotomies. The present patient had no history of alcohol intake or icterus, and TIBC was decreased. Though the possibility of primary liver disease seems remote, it can only be excluded by liver biopsy and HLA studies.

Iron overload can also occur secondary to anemias associated with ineffective erythropoiesis, for example, thalassemia, sideroblastic anemia or longstanding megaloblastic anemia It may or may not may be associated with blood transfusions or oral iron intake. The clinical presentation may resemble idiopathic hemochromatosis. The cause is increased plasma iron turnover, which sends inappropriate message to small intestinal mucosa and leads to hyperabsorption of dietary iron. Absence of anemia and normal peripheral smear rule out this possibility in the present case.

Porphyria cutanea tarda (PCT) is associated with mild iron overload[8]. Infact the skin mainfestations of PCT tend to occur in the presence of iron overload and remit with removal of excess iron by phlebotomy. Increase in iron stores is generally modest (<2g), unlike idiopathic hemochromatosis, Very few patients of idiopathic hemochromatosis have been reported to have increased urine porphyrins which may or may not be associated with clinical manifestations of PCT. It has also been postulated that inheritance of a single gene for HLA-linked hereditary hemochromatosis may be responsible for the hepatic siderosis seen in PCT[4]. Absence of clinical manifestation of PCT and presence of large iron overload in this patient supports the diagnosis of idiopathic hemochromatosis.

Rarely, chronic ingestion of iron in absence of any other disease may lead to secondary iron overload. It is reported to occur in Bantu tribe of Africa who consume alcoholic beverage rich in iron. Iron overload may also occur very rarely after chronic intake of medicinal iron. However no such history was present in this patient.

The most likely diagnosis in this patient is idiopathic hemochromatosis. This is an inborn error of metabolism, which results in iron load because of increased absorption of dietary iron from the small intestine. The mode of inheritance is autosomal recessive and histocompatibility antigens A3, B14and B7. Although HLA A3 is fairly common in general population (approx. in 30%), it is present in 70% of individuals homozygous for hemochromatosis. The gene frequency in the general population is as high as 5.6%. Prevalence of the disease is lower than theoretically expected from this gene frequency. The homogygotes have full clinical expression of the disease, where as the heterozygotes do not manifest clinically and have degrangements of iron metabolism in between the homozygotes and the normal persons.

There is excessive deposition of iron in various body tissues especially liver, heart, pancreas, endocrine glands, skin, joints, spleen and kidneys. The disease is rare in India[1,5,6], because of low iron content in Indian diet. The prevalence is less in females as women lose iron during menstruation and pregnancy.

Increased in attenuation of liver on CT abdomen (>36-40H.U.) is virtually pathognormic of idiopathic hemochromatosis. Only other condition in which it is increased is glycogen storage disease, and this can be distinguished by dual energy CT scanning. The constellation of symptoms seen in this patient can all be explained by the diagnosis of idiopathic hemochromatosis. Breast atrophy and loss of axillary and pubic hair is because of hypogonadism which generally is due to hypopituitarism. Low values of LH and FSH in a menopausal woman with undetectable estradiol, and inadequate response of prolactin to TRH support this view.

Diabetes occurs in approximately 60% of idiopathic hemochromatosis[8]. In majority symptoms of diabetes precede other manifestations of hemochromatosis. In the remaining 35% other manifestations of hemochromatosis precede onset of diabetes by an average of 5.6 years; although in very few of these patients diagnosis of hemochromatosis is made prior to

the onset of diabetes. Diabetes mellitus in idiopathic hemochromatosis may be due to (i) pancreatic islet cell damage subsequent to iron deposition (ii) cirrhosis leading to impaired glucose tolerance and diabetes (iii) coinheritance of diabetes along with alleles for hemochromatosis. Twenty five per cent of hemochromatosis with diabetes have first degree relative with diabetes, as compared to 4% of the non-diabetic hemochromatosis. Thus, diabetes occur more frequently in those patients with hemochromatosis who have positive family history of diabetes mellitus.

Management of diabetes is along the conventional lines ranging from dietary therapy only, with or without oral hypoglycemic drugs or insulin injections. The incidence of insulin resistance or fat atrophy is more as compared to idiopathic diabetes. Reducing body iron stores by phlebotomy improve glucose tolerance in 40% of the patients. No clinical or biochemical parameter can predict which patient is going to show improved glucose tolerance after phlebotomies, except that most of the patients who show improvement give no family history of diabetes. With prolongation of survival of patients with hemochromatosis, it seems that there is no difference in the incidence of complications of diabetes in this group of patients as compared to idiopathic diabetes.

Admission diagnosis : Diabetes mellitus, diabetic ketoacidosis, pulmonary tuberculosis, Addisonian crisis.

Clinical diagnosis : Idiopathic hemochromatosis, "secondary" diabetes mellitus-insulin dependent, hypopituitarism, diabetic ketoacidosis, pulmonary tuberculosis.

Pathological discussion

Liver biopsy was done in the patient and revealed increased stainable iron pigment in hepatocytes and sinusoidal cells. Portal tracts showed fibrosis with bile duct proliferation. No definite nodule was seen; there was no evidence of cirrhosis. No granuloma was demonstrated. Increased iron deposition in parenchymal cells in liver confirms the diagnosis of idiopathic hemochromatosis. Deposition of iron is predominantly in parenchymal liver cells in idiopathic hemochromatosis, as compared to condition of secondary iron overload due to transfusion or administration of iron preparations in which siderosis is more marked in reticuloendothelial system.[2] Iron accumulates in the lysosomes of the cells, and leads to formation of free radicles which damage the membranes, releasing lysosomal enzymes and thus causing tissue damage. Early damage to the liver leads to perilobular fibrosis with bile duct proliferation. Later cirrhosis ensues. The fibrosis decreases with removal of excess iron stores by phlebotomy; but cirrhosis is irreversible. The later category of the patient may progress to develop hepatocellular carcinoma, a major cause of mortality in idiopathic hemochromatosis.

It is important to screen the living relatives of the patient for disturbance of iron metabolism. If iron overload is found, instituting phlebotomy therapy prevents clinical manifestations of idiopathic hemochromatosis. Such subjects in which phlebotomy is started early have normal life expectancy.

Pathological diagnosis : Idiopathic hemochromatosis.

References

1. Bothwell TH, Charlton RW, Motulsky AG: Idiopathic hemochromatosis. In Stanbury JB, Wyngaarden JB, Frederickson DS, Goldstein JL, Brown MS (Eds). The metabolic basis of inherited disease. Me Graw Hill 1983: 1269-98.

2. Powell LW, Isselbacher KJ et al : Hemochromatosis. In Braunwald E et al (Eds). Harrison's Principles of internal medicine 11th ed. Me Graw Hill 1987 : 1632-5.

3. Milder MS, Cook JD, Stray S, et al: Idiopathic hemochromatosis, an interim report. Medicine 1980; 59 : 34-49.

4. Kushner JP, Edwards CQ, Dadone MM et al. Heterozygosity for HLA linked hemochromatosis as a likely cause of the hepatic siderosis associated with sporadic porphyria cutanea tarda. Gatroenterology 1985; 88 ; 1232-8.

5. Mithal A, Mulchandani J, Ammini AC et al : Idiopathic hemochromatosis: A report of two cases. J Ass Phys India 1988; 36 : 521-2.

6. Seshadri MS, Dayal AK, Bhaktavism A. Hepatome in hemochromatosis. J Ass Phys India 1982; 30 : 333-36.

7. Gollan JL. Diagnosis of hemochromatosis (Editorial) Gastroenterology 1983; 84 : 418-21.

8. Dymock IW, Cassar J, Pyke DA et al: Observations on the pathogenesis, complications and treatment of diabetes in 115 cases of hemochromatosis. Am J Mod 1972; 52 : 203-10.