Hemochromatosis is a disorder of chronic iron overload associated with tissue injury resulting from iron deposition. Typical findings include cirrhosis of liver, a bronze-brown pigmentation of the skin, diabetes mellitus, and cardiomyopathy. We describe a 46-year-old female patient presented with generalized bronze-brown pigmented skin with prominence over sun-exposed area for about 10 years. Diabetes mellitus and chronic hepatitis C history were traced, and she denied blood transfusion, medical or dietary iron ingestion. Increased serum iron and ferritin level accompanied with elevated transferrin saturation and hepatomegaly were investigated. The histopathologic study of skin showed hyperpigmentation in the basal layer of the epidermis. Iron stain revealed blue-staining granules mainly around blood vessels. More diffuse deposits of hemosiderin of liver tissue were also found. Lightening skin pigmentation was found after treatment with phlebotomy, chelating agent and regular insulin injection for 16 months. We herein present this case and review the literature. (Dermatol Sinica 22: 333-337, 2004)

Key words: Hemochromatosis, Pigmentation, Hemosiderin, Iron stain

Blood iron overload is a disease caused by excessive iron accumulation in the body, leading to tissue damage. Typical findings include liver cirrhosis, bronze-brown pigmentation of the skin, diabetes mellitus, and cardiomyopathy. We report a 46-year-old female patient who presented with generalized bronze-brown pigmented skin with prominence over sun-exposed areas for about 10 years. Diabetes mellitus and chronic hepatitis C history were traced, and she denied blood transfusion, medical or dietary iron ingestion. Increased serum iron and ferritin levels accompanied by elevated transferrin saturation and hepatomegaly were investigated. Histopathologic examination of the skin showed hyperpigmentation in the basal layer of the epidermis. Iron stain revealed blue-staining granules mainly around blood vessels. More diffuse deposits of hemosiderin in liver tissue were also found. Lightening skin pigmentation was found after treatment with phlebotomy, chelating agent, and regular insulin injection for 16 months. We present this case and review the literature.
INTRODUCTION

Hemochromatosis is a disorder of chronic iron overload associated with tissue injury resulting from iron deposition. The classic tetrad of hemochromatosis consists of hepatic cirrhosis, diabetes mellitus, hyperpigmentation of the skin, and cardiac failure. Histologically, siderosis around eccrine glands appears specific for hemochromatosis. We herein report a case of hemochromatosis.

CASE REPORT

A 46-year-old female suffered from generalized bronze-brown pigmentation over whole body surface area with progressive course for more than ten years. She was known to have history of chronic hepatitis C for many years and underwent operation for endometriosis in Oct. 1990. She also received oral hypoglycemic agents for control of diabetes at our outpatient department regularly since Jul. 2002. She denied ethanol consumption, blood transfusion or exogenous iron intake in the past. There was no known family history of similar manifestations.

Physical examination revealed hepatomegaly and generalized bronze-brown pigmentation over whole body surface. Slightly pronounced darkening was noted over sun-exposed area without mucosal involvement. No onychodystrophy was noted (Fig 1a & 1b).

Laboratory investigations were as the following: GOT: 71 u/l (10-35), GPT: 100 u/l (10-40), fasting sugar: 160 mg/dl (65-109), HbA c: 8.2% (4.0-5.2), positive anti-HCV antibody, serum iron: 194 µg/dl (55-180), ferritin: 6040 ng/ml (30-300), transferrin saturation: 92.8% (20-50), unsaturated iron binding capacity: 15 µg/dl (130-300), hepatic iron concentration: 388 µmol/g (3.6-28.6; dry weight), hepat-
ic iron index: 8.4 (<1.0). The following values were within the normal range: hemoglobin, MCV, ceruloplasmin, cortisol, thyroid and pituitary function test and tumor markers (αFP, CEA). Radiological studies including X-ray, CT, MRI and sonography showed no remarkable findings except hepatomegaly.

Histopathological examination of the skin biopsies, taken from the forearm and the abdomen, showed hyperpigmentation in the basal layer of the epidermis (Fig 2a). Hemosiderin demonstrated as blue-staining granules with iron stain was found mainly around blood vessels (Fig 2b), eccrine glands and within macrophages surrounding these glands (Fig 2c). More hemosiderin deposits of liver tissue was also found (Fig 2d).

On the basis of clinical manifestations, laboratory data, radiological investigations and histopathological findings, diagnosis of hemochromatosis was established. The patient received treatment including bi-weekly phlebotomy of 250 ml, subcutaneous infusion of deferoxamine 1500 mg (20-40 mg/kg/day) using a portable pump in eight hours daily, and insulin injection regularly. The decline of serum ferritin level (1284 ng/ml) and regressed skin pigmentation (Fig 1c & 1d) were noted after treatment for 16 months.

DISCUSSION

Hemochromatosis results from the development of an iron-overloaded state within parenchymal tissue with eventual tissue damage and impaired function of organs, especially the liver, pancreas, heart, joints and pituitary gland. The classic tetrad of manifestations consists of hepatic cirrhosis, diabetes mellitus, hyperpigmentation of the skin and cardiac failure. Other systemic signs include arthritis, gonadic and thyroid deficiency. The symptoms usually first developed between ages 40 and 60 in nearly 70% of affected patients. The disease is rarely evident before age 20.

The progressive accumulation of iron within tissues is thought to increase the formation of reactive oxygen species (ROS), through Fenton reaction. ROS may interact with proteins, lipids and DNA, which results in formation of peroxides, mitochondria damage, release of lysosomal enzymes into the cytosol, damage of DNA and enzymes, and progressive loss of membrane potential resulting in cell death.

The generalized hypermelanosis observed in 90 to 98 percent of cases may be bronze, blue-gray, or brown black, so hemochromatosis is also called bronzed diabetes. There is accentuation of pigmentation over sun-exposed areas of skin, however, hyperpigmentation also may involve genitalia, flexor folds, scars, and nipples. The changes are attributed to deposition of melanin (brown) and hemosiderin (blue black). Cutaneous and mucous membrane involvement, seen in 15 to 25 percent, may resemble the pigmentation in Addison's disease. Histology of pigmented skin shows increased melanin in the basal layer of the epidermis. Hemosiderin demonstrated as blue-staining granules with iron stain, mainly around blood vessels, the basement membrane zone of the sweat glands and within macrophages surrounding the glands.

Siderosis around eccrine glands appears specific for hemochromatosis. This location is not observed in normal individuals where iron deposits are visible only in apocrine sweat glands. The iron accumulated in skin stimulates melanocytic activity either by increasing oxidative processes or by reacting with epidermal sulfhydryl groups and reducing their inhibitory effect on the enzyme system governing melanin synthesis. Skin pigmentation seemed to accentuate during exacerbations and regress several months after initiation of treatment.

Other cutaneous signs including atrophy, ichthyosis-like changes, alopecia, koilonychia, onychonychia, leukonychia, spider angiomas, palmar erythema, lipodystrophy and cutaneous porphyria, had been reported in hemochromatosis, but not seen in our patient.

In the absence of other known causes of iron overload related to hepatic cirrhosis, alcohol abuse, viral hepatitis, or iron loading anemias, the currently accepted criteria for diagno-
sis of established hemochromatosis include at least one of the followings: (1) stainable hepatic iron grade 3 or 4, (2) hepatic iron concentration >80 μmol/g (dry weight), (3) hepatic iron index > 1.9, (4) at least 5 g iron removed by phlebotomy without inducing iron deficiency. Other abovementioned suspicious clinical manifestations and biochemical associations, ie, serum ferritin >350 μg/l in men, >250 μg/l in women, serum iron >150 μg/dl, and a fasting serum transferrin saturation persistently >45%. Liver biopsy remains the gold-standard diagnostic test for hemochromatosis. However, its role has been changed to mainly one of prognostic value for confirming or staging of cirrhosis since the elucidation of the HFE gene for genetic hemochromatosis. Hepatic iron concentration and hepatic iron index, which can be helpful in the distinction between secondary iron overload and hereditary hemochromatosis (hepatic iron index is 1.9 or more). High values of hepatic iron concentration and hepatic iron index (388 μmol/g & 8.4) of the patient were noted. Therefore, hereditary or homozygous hemochromatosis is favored by Summers’ definition. Although hepatitis can result in iron overload, the accumulation is minimal when compared to those with HFE mutation. In chronic hepatitis C patients without HFE mutation, liver iron accumulation is mild (<3-fold above the upper limit of hepatic iron concentration). However, iron can act synergistically with HCV to enhance liver damage.

Addison’s disease, ACTH producing tumors, phytophotodermatitis, polymorphous light eruption, poikiloderma of Civatte, Riehl melanosis, postinflammatory hyperpigmentation, argyria and drug-induced hypermelanosis should be included for differential diagnosis.

Women are affected at a later age than men, possibly because of physiologic blood loss from menstruation and parturition, limiting the rate at which excess iron is accumulated. The degree of iron overload has a direct affect on the life expectancy of the individual with hemochromatosis. In male patients with hemochromatosis and cirrhosis, a 200-fold increased incidence of hepatocellular carcinoma has been documented, and accounts for 75 percent of hemochromatosis-related deaths.

The strategy of treatment is to remove the excess body iron and to give supportive treatment of damaged organs. Once the diagnosis of hemochromatosis has been made, therapeutic phlebotomy of 500 ml should be performed once to twice weekly until ferritin levels less than 50 μg/l and transferrin saturation 50% or less, with regular monitoring of hemoglobin or hematocrit and serum ferritin levels after each gram of iron removed (one 500-ml unit of blood contains 200 to 250 mg iron). Total accumulated amount of 5600 ml patient’s blood was removed by receiving bi-weekly phlebotomy of 250 ml after diagnosis. Maintenance phlebotomy is performed three to four times yearly to maintain ferritin levels at less than 50 μg/l. The institution of phlebotomy therapy before the onset of cirrhosis and/or diabetes significantly reduces the morbidity and mortality in patient with hemochromatosis. Chelating agents such as deferoxamine are indicated when anemia or hypoproteinemia is severe enough to preclude phlebotomy. The patient received subcutaneous infusion of deferoxamine using a portable pump daily for 16 months. The patient was advised to avoid iron supplementation, red meat and alcohol abuse. Large doses of vitamin C should also be avoided because vitamin C facilitates the absorption of iron. Raw shellfish should also be avoided since several cases of fatal infection with V. vulnificus has been reported in patients with hemochromatosis.

Early diagnosis and the consequent suitable treatment are crucial: many of the manifestations are reversible and life is not shortened if iron stores are normalized before the development of diabetes or cirrhosis. Therefore hemochromatosis should be considered for patients presenting with generalized hyperpigmentation.

REFERENCES