Case Report

Correlation between the Depth of Inverted T Waves and the Serum Level of Ferritin in a Deferoxamine-treated Patient with Primary Hemochromatosis and Hyperthyroidism

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A 74-year-old female having primary hemochromatosis and hyperthyroidism is described. The initial ECG showed sinus rhythm, and depression of ST segments and inversion of T waves in I, II, III, aVF, and V4-6. By deferoxamine and propylthiouracil, the serum level of ferritin was decreased from 4,500 ng/ml to 440 ng/ml in a period of 6 months. The thyroid function was also returned to normal. After cessation of both drugs, the serum ferritin level increased gradually reaching a level of 3,100 ng/ml in the next 15 months but the thyroid function remained normal. During and after the deferoxamine administration, the depth of inverted T waves became more shallow and gradually deeper again, respectively. There seemed to be a correlation between the depth of inverted T waves and the serum level of ferritin. It was, however, unlikely that toxic iron may have induced the hyperfunction of the thyroid gland.

Key Words: Cardiac hemochromatosis, Cardiomyopathy, Chelation therapy

Cardiac involvement is often seen in hemochromatosis (1, 2). While the mechanism of cardiomyopathy is not entirely clear, it was reported that repeated venesection (3-12) and chelation therapy (13-17) are of benefit leading to relief of symptoms and restoration of cardiac function. In cardiac hemochromatosis, various kinds of alteration on electrocardiogram (ECG), such as low voltage, atrial and ventricular arrhythmias, conduction blocks, and ST-T changes are observed (1, 2, 8-18). In addition, the thyroid gland is one of the affected organs and its involvement is usually manifested as hypothyroidism (3, 19).

In this communication, we describe a case of primary hemochromatosis and hyperthyroidism, in which the depth of inverted T waves noted on the initial ECG became more shallow during deferoxamine administration and gradually deeper again after cessation of the therapy. It was likely that there was a correlation between the depth of inverted T waves and the serum level of ferritin.

CASE REPORT

A 74-year-old Japanese female was referred to our hospital in December 1985 for treatment of hemochromatosis and hyperthyroidism. She had been well until September 1985 when she complained of fatigue and palpitation. She had no episode of blood transfusion and oral iron ingestion. The history of other members of her family was non-contributory. She had 3 sisters and a brother, but

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no children. There was not a consanguineous marriage. On admission to our hospital, the patient was a thin, chronically ill female. The height was 143.5 cm and the body weight was 29.0 kg. Pulse was 92/min and regular, and blood pressure was 150/50 mmHg. The skin was grey and thyroid gland was slightly enlarged. The liver was palpable 2 cm below the right costal margin. The physical examination was otherwise unremarkable. No cardiomegaly was noted on a chest x-ray film (cardiothoracic ratio 50%). No valvular diseases were recognized on echocardiography. The ECG, as shown in Figure 1, revealed sinus rhythm, and depression of ST segments and inversion of T waves in I, II, III, aVF, and V4-6. Computerized tomography showed increased density of the liver.

Fig. 1. ECG on admission to our hospital (December 1985).

The blood counts were: hemoglobin 149 g/l, RBC $4.45 \times 10^{12}$/l, PCV 48.4, platelet $319 \times 10^9$/l, and WBC $7.1 \times 10^9$/l with a normal differential. Serum iron was 170 $\mu$g/dl (normal 70-110) and total iron-binding capacity was 238 $\mu$g/dl (250-400). Percent transferrin saturation was 71.4%. The serum level of ferritin was 5,800 ng/ml (3-120). The results of liver function tests were: SGOT 62 U (5-35), SGPT 65 U (5-30), LDH 282 U (50-400), alkaline phosphatase 13.5 U (2.7-10.0), total bilirubin 0.5 mg/dl, $\gamma$-glutamyltranspeptidase 112 mU/ml (0-40), and total cholesterol 170 mg/dl (130-230). Total serum protein was 6.0 g/dl with 51.0% albumin. The renal function was normal. Serum electrolytes were: Na 142 mEq/l (134-153), K 4.2 mEq/l (3.5-5.0), Cl 108 mEq/l (98-108), Ca 9.2 mg/dl (9.0-10.0), and P 4.3 mg/dl (2.7-4.7). The thyroid function tests revealed: T4 15.5 $\mu$g/dl (4.5-13.0), free T4 4.78 ng/dl (0.85-2.15), T3 280 ng/dl (80-180), free T3 1.08 ng/dl (0.30-0.58), reverse T3 125 ng/dl (190-375), and TSH < 1.3 $\mu$U/ml (< 8.0). Antimicrosomal antibodies were detected.

Glucose tolerance was slightly impaired with a fairly good insulin response to 75 g glucose ingestion. An intramuscular administration of 0.5 g deferoxamine resulted in excretion of 4.6 mg iron during the following 24 hours, while the baseline value was less than 0.4 mg. A liver biopsy revealed massive iron deposits in the parenchymal cells of the liver. Such iron deposits were also demonstrated in the bone marrow cells but not in biopsied skin specimens. From these findings, she was diagnosed as having primary hemochromatosis and hyperthyroidism. Additionally, HLA haplotypes were A24(9), BW54(W22), BW61(40), and CW3.

As the patient was thin and exhausted, it was thought that she would not tolerate repeated venesection. Thus, in March 1986, she began deferoxamine 1 g/day intravenously and propylthiouracil 150 mg/day orally (Figure 2). The thyroid function was returned to normal in June 1986. As she developed congestive heart failure and bacterial pneumonia at the end of September 1986, the deferoxamine and propylthiouracil were discontinued. She was improved by digoxin and furosemide. A total of 165 g deferoxamine was given to this patient within the 6 months. During this period of time, the serum level of ferritin was rapidly decreased from 4,500 ng/ml (March 1986) to the lowest determination 440 ng/ml in September 1986.

![Fig. 2. Clinical course. Normal ranges are: ferritin 3-120 ng/ml; T3 80-180 ng/dl (hatched area); T4 4.5-13.0 $\mu$g/dl (hatched area).](image-url)
The depth of inverted T waves in V5 and V6 became gradually more shallow. After cessation of deferoxamine, the depth of T waves was deepened (Figure 3). The serum level of ferritin also began to increase proportionally. However, the thyroid function remained normal. In December 1987, the serum levels of ferritin, T4, and T3 were 3,100 ng/ml, 6.7 μg/dl, and 50 ng/dl, respectively. During the disease course, the liver function tests showed unchanged and the serum electrolytes were all within normal ranges.

**DISCUSSION**

In this case, it seemed that the depth of inverted T waves in I, II, III, aVF, and V4-6 changed in parallel with the serum level of ferritin. It was, however, unlikely to attribute the change in T waves to hyperthyroidism as while the serum levels of ferritin, T4, and T3 were proportionally decreased by the simultaneous administration of deferoxamine and propylthiouracil, the thyroid function remained normal after cessation of both drugs.

Buja and Roberts detailed that the myocardial iron overload is responsible for ventricular dilatation and increase in wall thickness (2). It was reported that cardiac symptoms as well as functions determined by echocardiographic and catheterization findings were recovered by repeated venesection and deferoxamine therapy (3-17). Grisaru et al. stated in β-thalassemia patients that frequent blood transfusion combined with chelation therapy reduced left ventricular dilatation and wall thickness and those changes corresponded to the serum ferritin level (16). Thus, the cardiac change can be reversible.

It was reported that ST-T change was observed in nearly 50% of cases of hemochromatosis (18). While the cardiac dysfunction can be reversible by appropriate therapies, there were few description on serial ECG change (4, 8, 9, 20). Grosberg described that there was no alteration on the inverted T waves in V1-5 in a patient successfully treated by venesection (4). In contrast, Jachuck et al. examined the cardiac state of 8 patients with idiopathic hemochromatosis (8). In one out of the 8 cases, initial ischemic change, shown as inversion of T waves, was improved by venesection (8). Charlton and Bothwell also described an improvement in ECG in a case after removal of 20 g iron by phlebotomy (20). Swan and Dewar reported a case of hemochromatosis, in which elevation of ST segment and inversion of T waves were seen in chest leads but postmortem examination revealed no abnormalities of coronary arteries (1). Hence, it may not be considered that the ST-T change in hemochromatosis is attributed to ischemic coronary disease.

Ferritin and heme iron do not damage cells. When the iron content is, however, over a critical level, the excessive iron then exists as forms of nonferritin and nonheme iron, doing the cells various injuries, such as increased microsomal lipid peroxidation, mitochondrial membrane damage, impaired mitochondrial oxidative phosphorylation, lysosomal fragility, and release of lysosomal enzymes (21, 22), Buja and Roberts documented that iron deposition is much more in epicardium than in endocardium (2). While clarified incompletely, it was reported that the appearance of inverted T waves is related to change in action potential duration between endocardial and epicardial layers of ventricle (23, 24). Thus, in our case, toxic iron present in the myocardium may have altered the action potential duration between endocardial and epicardial layers of myocardium. Hence, it may not be considered that the ST-T change in hemochromatosis is attributed to ischemic coronary disease.

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association between hemochromatosis and the histocompatibility antigens HLA-A3, B14, and B7. However, the HLA haplotypes of our case were A24(9), BW54(W22), BW61(40), and CW3. From the result of HLA typing and the history of other members of her family, genetic involvement would be ruled out in our case.

Primary hemochromatosis is rarely complicated with hyperthyroidism (25, 26). As to the mechanism of the thyroid dysfunction, two possibilities were assumed. Althausen and Kerr suggested stimulatory effect of hemosiderin deposits on thyroid function (25). Williams stated, on the other hand, that the presence of impaired hepatic function due to deposition of iron in the liver aggravated the thyroid toxicity (26). Unfortunately, in our case, a biopsy of the thyroid gland was not permitted. After cessation of both deferoxamine and propylthiouracil, reaccumulation of iron occurred but the thyroid function persisted normal. Since the liver function showed unchanged during the disease course, it was unlikely that the hyperthyroidism was due to either of the two mechanisms mentioned above.

REFERENCES