Transient Thyrotoxicosis After Unilateral Adrenalectomy in Two Patients with Cushing’s Syndrome

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Abstract

We found transient hyperthyroidism in the course of hydrocortisone withdrawal in two patients who had undergone unilateral adrenalectomy to resect cortisol-hypersecreting adenoma. A 38-yr-old woman showed clinical thyrotoxicosis 3 months after the operation. Serum T₄, T₃ and TBG levels were 11.9 μg/dl, 310 ng/dl and 16.5 μg/ml, respectively. She was given methimazole (MMI) 15 mg/day for 4 weeks. After the cessation of MMI treatment, she eventually recovered to the euthyroid state. The other patient, a 34-yr-old man showed very mild clinical symptoms of hyperthyroidism 2 months after the operation. Serum T₄, T₃ and TBG levels were 10.4 μg/dl, 240 ng/dl and 14.5 μg/ml, respectively. In this case, no antithyroid drug was given. Two to three months after the onset of hyperthyroidism, he returned to the euthyroid state spontaneously. We carefully eliminated the possibility of factitious thyrotoxicosis in both cases. They had neither neck pain nor fever. Both had low radioactive iodine uptake by the thyroid. Therefore, we diagnosed them as painless thyroiditis induced after the resection of hypersecreting adrenal adenoma.

Transient thyrotoxicosis has been reported in patients with subacute thyroiditis (Volpe et al., 1958), painless thyroiditis (Woolf and Daly, 1976), postpartum transient thyrotoxicosis (Amino et al., 1976), and silent thyroiditis (Nikolai et al., 1980). It is considered to be destruction-induced thyrotoxicosis. Whether or not it is associated with neck pain, the thyroidal radioactive iodine uptake is usually very low. It almost always undergoes spontaneous remission and sometimes passes through the euthyroid and then the hypothyroid state.

Recently, Maruyama et al., (1982) reported a patient with rheumatoid arthritis who showed transient hyperthyroidism after the cessation of long-term therapy with adrenocorticosteroid. The patient was histologically ascertained to have chronic lymphocytic thyroiditis. They thought that the thyrotoxicosis was induced by withdrawal of the steroid hormone which had an immunosuppressive action.

In this report, we present similar evidence in two cases which showed transient thyrotoxicosis induced by the escape from long-
term hyperadrenocorticism due to Cushing's syndrome.

**Material and Methods**

Serum T₄, T₃, free thyroxine (FT₄), free triiodothyronine (FT₃), TSH and thyroxine-binding globulin (TBG) were determined by radioimmunoassay using commercially available kits. Gamma Coat free T₄ RIA kits and Amerlex free T₃ RIA kits were used. The normal ranges of T₄, T₃, FT₄, FT₃ and TBG are 6-12 µg/dl, 80-180 ng/dl, 0.8-2.0 ng/dl, 3.0-5.3 pg/ml and 18.6-25.0 µg/ml, respectively. The normal range for TSH is below 5 µU/ml. Thyroid antibodies were determined by thyroglobulin-coated and microsome-coated tanned sheep red cell hemagglutination technique, using commercially available kits. The 24-hr thyroidal uptake of ¹³¹I was measured by the standard procedure with normal values from 15 to 40%. TSH-receptor antibody (TRAb) titer was determined with a Smith's kit (Schewring and Smith, 1982).

**Case Report**

**Case 1**

A 38-yr-old woman was admitted to the hospital because of obesity and pretibial edema. She was well until 2 years earlier, when she first noticed the edema on her face and lower legs. She also noticed unusual acne on her face and chest. Just before admission to hospital, she noted several episodes of palpitation and chest pain. Physical examination revealed that she had central obesity, moon face and mild exophthalmos. Her blood pressure was elevated (160/110 mmHg). The thyroid gland was not enlarged. Her plasma cortisol level at 7.00 a.m. was 17.8 µg/dl and the circadian rhythm was abolished. Prior administration of 1 mg dexamethasone did not suppress the plasma cortisol next morning. Her urinary 17-OHCS was high (13.5 mg/day) and 17-KS was normal (4.9 mg/day). A left adrenal tumor was ascertained by whole body CT-scan and ¹³¹I-cholesterol adrenal scintigram. Serum T₄, T₃ and FT₄ were normal and TSH response to TRH was within the normal range. An electrocardiogram disclosed slight ST-depression in leads 1 and 2, and strain patterns in V₅, V₆ and V₇. RA test was 1+. Antithyroglobulin antibody titer was 1600× positive, but no antimicrosomal antibody was detected. She underwent left adrenalectomy on May 9, 1981. Histological examination revealed a mixed type adenoma composed of clear cells and compact cells.

By the end of June, the dose of hydrocortisone was gradually reduced to 20 mg/day, when she felt arthralgia and morning stiffness in her fingers. On physical examination, her pulse rate was 92/min, the thyroid was enlarged to three times the previous size and the consistency had increased. Serum T₄, T₃ and TSH were 11.9 µg/dl, 310 ng/dl, and 1.3 µU/ml, respectively. Hydrocortisone was further reduced to 10 mg/day. By the next visit on August 18, 1981, she had developed clinical manifestations of thyrotoxicosis such as finger tremor and excessive sweating. She complained of general lassitude and joint pain when moving fingers and knees. The Serum FT₃ was increased to 7.4 pg/ml, TRAb was negative (−18) and the TBG concentration was 16.5 µg/ml. RA was 3+, antimicrosomal antibody was 400× positive, antithyroglobulin antibody was 6400× positive and twenty-four-hr ¹³¹I thyroidal uptake was only 3.2%. MMI was prescribed on September 1, and continued for 1 month. By the middle of December, serum T₄ and T₃ returned to near the normal range (Fig. 1).

**Case 2**

A 34-yr-old man visited our hospital because of obesity and general lassitude. About one year before the visit, he noticed that his extremities had begun to become slender although his body weight had increased. Then, just before his visit, he also noticed muscular weakness and felt...
difficulty in climbing stairs. He had been on antihypertensive drug for 2 years. On physical examination, central obesity and very mild exophthalmos were noted. The thyroid gland was not enlarged and no cutaneous striation was found. Proximal muscular weakness and slight muscular atrophy were observed in his extremities. His blood pressure was 180/110 mmHg. The plasma cortisol level was high and circadian rhythm was completery absent (28.9 μg/dl and 7.00 a.m., 28.8 μg/dl at 3.00 a.m., 22.0 μg/dl at 11.0 p.m.). The plasma cortisol level was suppressed neither by 2 mg/day p.o. for 3 days nor by 8 mg/day p.o. for 3 days dexamethasone administration. These endocrinological data were compatible with Cushing's syndrome due to adrenal tumor. CT-scan revealed a left adrenal mass. Serum T₄, T₃ and FT₃ were 7.8 μg/dl, 74 ng/dl and 3.0 μg/ml, respectively. TSH was 1.0 μU/ml. TBG was decreased to 13.0 μU/ml. TRAb was negative (−6). He underwent left adrenalectomy on November 14, 1981. Histological examination revealed a adenoma composed of compact cells rich in lipofuscin granules. About one month after the operation, serum level of thyroid hormones began to rise. Both serum T₃ and FT₃ were 200 ng/dl and 6.0 pg/ml, respectively. He had been on 40 mg hydrocortisone/day. At the next visit in January, 1982, he was noticed to have moist skin, but otherwise appeared well. During the succeeding follow-up period he showed a couple of symptoms of thyrotoxicosis such as excessive sweating and finger tremor. He had neither thyroid enlargement nor tenderness. No increase in the consistency of the thyroid was found. The surreptitious use of thyroid hormone was carefully excluded by examining his history. Serum T₄ was 10.4 μg/dl and T₃ was abnormally high and gradually returned to normal. Serum T₄ once returned to 7.6 μg/dl and then gradually increased with a concomitant increase in TBG, but remained within the normal range. Twenty four hr ¹³¹I thyroidal uptake was only 6.5%. Repeated examination of antithyroglobulin and antithyroid microsomal antibody were negative in this case. No antithyroid drug was prescribed (Fig. 2).
Discussion

Usually, thyrotoxicosis is due to the overfunctioning thyroid gland, the cause of which may exist in the thyroid gland itself or may be due to TSH or some other thyroid stimulators (Adams and Purves, 1956; Adams and Kennedy, 1967; Onaya et al., 1973).

There exists another type of thyrotoxicosis due to destruction of the thyroid gland caused by thyroiditis. The latter is characterized by the short course of its clinical signs. Most of them are reported to pass from a hyperthyroid state to a euthyroid state or, occasionally, to a hypothyroid state (Solen et al., 1984). It is now considered that the low thyroidal $^{131}$I uptake is the best indicator to use in differentiating the latter from the former. Almost all cases so far reported with transient thyrotoxicosis induced by the destructive change were known to be associated with low thyroidal $^{131}$I uptake (Woolf and Daly, 1976; Papaterou and Jackson, 1975). As far as we know, the presence of abnormal thyroid stimulators which cause only the release of thyroid hormones without elevating thyroidal iodine uptake has not hitherto been reported. Therefore our patients seem to have had some kind of destruction-induced thyroiditis, probably painless thyroiditis.

Gluk et al., (1975) described the histological findings of thyroid biopsy specimen obtained from patients with painless thyroiditis. Histological studies were not performed in our patients, but the existence of antithyroid antibodies and increased consistency of the thyroid gland without tenderness indicate underlying lymphocytic thyroiditis in case 1. In case 2, antithyroid antibodies were not detected, so there is no evidence of underlying lymphocytic thyroiditis. Inada et al. (1981), however, reported a patient with transient hyperthyroidism due to painless thyroiditis who did not have antithyroid antibodies, but slight lymphocytic infiltration into the thyroid was detected in the biopsy specimen.

A decreased $T_3/T_4$ ratio is also submitted as a useful indicator in differentiating the destruction-induced thyrotoxicosis from Graves' disease (Amino et al., 1981). In our cases, $T_3/T_4$ ratio were over 20 and were not compatible with the previous reports. This discrepancy may be partially explained by decreased TBG concentration caused by long-term hypercorticism (Oppenheimer and Werner, 1966). It is said that decreased TBG causes the $T_3/T_4$ ratio to increase (Larsen, 1972). Therefore, the $T_3/T_4$ ratio is not a reliable indicator in such cases as ours. Low TSH levels and negative TRAb titers, as Onaya et al., (1983) suggested, are also compatible with painless thyroiditis.

The incidence of the association of Cushing's syndrome with chronic lymphocytic thyroiditis has not often been reported. It is known that the glucocorticoid suppresses the peripheral conversion of $T_4$ to $T_3$ (Burr et al., 1975) and induces the disappearance of long-acting thyroid stimulator (Snyder et al., 1964). It is also known that the adrenal steroid suppresses TSH secretion (Visser and Lambert, 1981) and the activity of Graves' disease (Williams et al., 1975). On the other hand, Volpe et al. (1978) pointed out that Graves' disease has been initiated in the course of steroid therapy, and assumed a connection between its occurrence and the T-lymphocyte suppressive effect of the steroid. Blizzard et al., (1962) used a quantity of steroid hormone in patients with Hashimoto's disease, and observed a decrease in the titer of the antithyroid antibody. They are the changes caused by the immunosuppressive effect of the steroid hormone leading to cessation of the destructive changes in Hashimoto's thyroiditis. Considering all of these, the transient thyrotoxicosis after the resection of adrenal cortisol-hypersecreting tumor in patients with lymphocytic thyroiditis appears to be a not unusual sequel.
Maruyama et al. (1982) have recently reported a transient thyrotoxicosis which occurred after the cessation of steroid therapy in a patient with autoimmune thyroiditis and rheumatoid arthritis. It is of interest to note that there is much similarity between their case and ours. It seems proper to say that this type of transient thyrotoxicosis is one of the steroid withdrawal syndrome. The mechanism of this syndrome, however, remains to be investigated further.

References


