Simultaneously Found Transient Hypothyroidism due to Hashimoto's Thyroiditis, Autoimmune Hepatitis and Isolated ACTH Deficiency after Cessation of Glucocorticoid Administration

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Abstract. We present a 42-year-old woman with concomitant transient hypothyroidism due to Hashimoto's thyroiditis, autoimmune hepatitis and isolated ACTH deficiency. Two months after ceasing prednisolone (5 mg/day) for uveitis, she was discovered incidentally to have liver dysfunction with hypergammaglobulinemia, later diagnosed as autoimmune hepatitis by histological examination of the biopsied liver. In addition, primary hypothyroidism due to Hashimoto's thyroiditis and secondary hypocortisolism due to isolated ACTH deficiency were revealed by endocrinological examination. Although not treated, her liver dysfunction and hypothyroid state recovered simultaneously, and the isolated ACTH deficiency was restored six months later. We concluded, after a needle-biopsy of the thyroid, that the transient hypothyroidism was due to Hashimoto's thyroiditis and the reversible ACTH deficiency was probably due to autoimmune hypophysitis. This case shows that cessation of steroid treatment may transiently exacerbate the polyglandular autoimmune syndrome.

Keywords: Hashimoto's thyroiditis, Autoimmune hepatitis, Isolated ACTH deficiency, Glucocorticoid, Polyglandular autoimmune syndrome

IT IS KNOWN that cessation of glucocorticoid therapy exacerbates preexisting autoimmune diseases [1], but the occurrence of autoimmune polyglandular failure simultaneous with glucocorticoid withdrawal is rare. We present a patient with polyglandular autoimmune (PGA) syndrome, including Hashimoto's thyroiditis, autoimmune hepatitis and isolated ACTH deficiency (due to probable autoimmune hypophysitis), a possible polyglandular failure after cessation of glucocorticoid therapy, which later recovered spontaneously.

Case Report

A 42-year-old woman was diagnosed as having uveitis in 1988, and was irregularly given 5 mg (once a day) prednisolone orally until March, 1992. The etiology of uveitis was unclear. Two months after ceasing prednisolone, she was incidentally discovered to have liver dysfunction with hypergammaglobulinemia. At this time, she was quite well and had no complaint. She was admitted on May 8, 1992 to our hospital for evaluation of liver dysfunction.

On admission, she was 154.5 cm tall and weighed 47.3 kg. She had irregular menstrual cycles. Blood pressure was 104/62 mmHg and the pulse rate 60/min. Consciousness was clear. The skin was normally moist and no pigmentation was observed.
A small diffuse goiter was palpable without any tenderness. There was no abnormal finding in the chest or abdomen. The liver and spleen were not palpable. Neurological examination revealed no abnormalities.

Laboratory data on admission were as follows: erythrocyte sedimentation rate 39 mm/h, erythrocyte count 464 × 10⁴/mm³, hemoglobin 13.4 g/dl, hematocrit 41.5%, leukocyte count 3,600/mm³, and platelet count 20.6 × 10⁴/mm³. The serum C-reactive protein was 0.4 mg/dl. Serum total protein was 9.5 g/dl, albumin 4.9 g/dl, γ-globulin 2.9 g/dl, total cholesterol 190 mg/dl, triglyceride 115 mg/dl, creatinine 0.6 mg/dl and blood urea nitrogen 14 mg/dl. The fasting plasma glucose was 92 mg/dl. Serum sodium was 136 mEq/l, potassium 4.8 mEq/l, chloride 104 mEq/l, calcium 9.4 mg/dl, and phosphorus 4.2 mg/dl. The serum aspartate aminotransferase was 99 IU/l, alanine aminotransferase 94 IU/l, alkaline phosphatase 510 IU/l, γ-glutamyl transpeptidase 160 IU/l, lactate dehydrogenase 340 IU/l, and total bilirubin 0.8 mg/dl. Hepatitis A viral antibody was positive, but the IgM type antibody was negative. On the other hand, hepatitis B and C viral markers were all negative. Immunologically, the RA test was negative and the IgG level was 4,193 mg/dl. Anti-smooth muscle antibody (ASMA), microsome test (MCHA), and thyroid test (TGHA) were all positive (ASMA × 640, MCHA × 6400, and TGHA × 100), but anti-nuclear antibody, anti-DNA antibody, anti-mitochondrial antibody, anti-adrenocortical antibody, and anti-pituitary antibodies were all negative. TGHA and MCHA were measured with Microtiter Particle Agglutination Test kit (Fujirebio inc., Tokyo, Japan). Anti-adrenocortical antibody was measured by an indirect immunofluorescence method at Biomedical Laboratory (Saitama, Japan) [2]. Anti-pituitary antibodies were measured with rat pituitary cytoplasmic antigens or pituitary cell surface antigens from GH₃ cells and/or AtT-20 cells at Biomedical Laboratory [3].

Endocrinological parameters were as follows: serum free thyroxine (FT₄) was 0.75 ng/dl (normal, 0.7–2.1 ng/dl), free triiodothyronine (FT₃) was 2.26 pg/ml (normal, 2.25–5.36 pg/ml), and TSH was 25.25 µU/ml (normal, 0.27–6.00 µU/ml). The TSH response to TRH was quite exaggerated, thus indicating the presence of primary hypothyroidism.

One month before admission, her thyroid function was euthyroid: FT₄, 1.26 ng/dl; FT₃, 3.70 pg/ml; and TSH, 0.63 µU/ml. Primary hypothyroidism developed one month after admission. Serum LH was 32.1 mIU/ml (normal, 0.6–16.8 mIU/ml), and FSH was 55.6 mIU/ml (normal, 1.6–19.0 mIU/ml). The increases in LH and FSH were probably due to her premenopausal state. Serum GH was 1.64 ng/ml (normal, <5 ng/ml). Plasma cortisol and ACTH at 0800 h were 7.1 µg/dl (normal, 4.5–24 µg/dl) and 16.4 µg/ml (normal, 4.4–48 µg/ml), respectively. PRL, LH, FSH, GH, and ACTH were measured by an immunoradiometric assay (PRL, LH and FSH, Daiichi Radioisotope Ltd., Tokyo, Japan; GH, Eiken Chemical Co. Ltd., Tokyo, Japan; ACTH, Nichols Institute Diagnostics, San Juan Capistrano, CA, USA), FT₄, FT₃ and cortisol by a radioimmunooassay (FT₄ and FT₃, Amersham Japan, Tokyo, Japan; cortisol, Eiken Chemical Co. Ltd.). TSH by a two-site immunoenzymometric assay (Tosoh, Yamaguchi, Japan).

Laparoscopic study showed a large white liver with depressions. A liver biopsy specimen revealed bridging necrosis, piecemeal necrosis, intralobular and portal mononuclear cell infiltrations, mainly plasma cells, which led to a histological diagnosis of chronic active hepatitis of probable autoimmune etiology (Fig. 1). The serum transaminase levels decreased spontaneously to normal one month after admission in association with the reduction in serum γ-globulin levels (Fig. 2). Serial liver biopsy specimens revealed that the intensity of autoimmune chronic active hepatitis had weakened.

Ultrasongraphy of the thyroid gland showed a diffuse goiter (estimated thyroid volume, 32.6 mm³). A needle-biopsy specimen of the thyroid gland showed diffuse lymphocytic thyroiditis with noticeable follicular destruction, leading to a histological diagnosis of Hashimoto's thyroiditis (Fig. 3). At one month after admission, the serum FT₄ and FT₃ levels had normalized spontaneously, but the serum TSH level remained above normal (Fig. 2). Radioactive iodine uptake was apparently high at 84% (normal, 10–40%), suggesting recovery from transient hypothyroidism due to Hashimoto's thyroiditis.

To explore the etiology of sustained mild eosinophilia (450/mm³), her adrenocortical function was repeatedly examined 3 weeks after admission.
Basal plasma cortisol at 0800 h was 2.7 μg/dl. The basal plasma ACTH at 0800 h (8.6 pg/ml) was at the lower limit of normal. Over the next 2 weeks, her plasma cortisol and ACTH at 0800 h were undetectable (Fig. 2), and their circadian rhythms were completely lost. Urinary excretion of 17-hydroxycorticosteroids (17-OHCS) and of free cortisol decreased to 1.8 mg/day (normal, 3.2-11.2 mg/day) and less than 3.0 μg/day (normal, 38.7-174 μg/day), respectively. There was no response in the plasma ACTH and cortisol to CRF (100 μg) stimulation, whereas other anterior pituitary hormones exhibited an almost normal response to the hypothalamic releasing hormones. The plasma ACTH was only minimally increased to 4.1 pg/ml after metyrapone 3 g/day for 2 days, while the plasma level of cortisol remained undetectable. These findings led to the diagnosis of secondary adrenal insufficiency due to isolated ACTH deficiency. Two months after admission, basal plasma ACTH increased slightly to the lower limit of normal, but CRF stimulation induced little response to ACTH. On the other hand, basal plasma cortisol remained undetectable (Fig. 2). A T1-weighted MRI performed in August, 1992 revealed almost no change in the pituitary gland. Six months later, plasma ACTH and cortisol levels at 0800 h gradually increased to normal under 5 mg prednisolone daily for autoimmune hepatitis.
pituatory deficiency was also inconsistent with a diagnosis of pituitary tumor; in tumor patients, GH and gonadotropin levels are generally reduced before those of ACTH and TSH [8]. In addition, the close parallel relationship of isolated ACTH deficiency to the other two autoimmune disorders provides strong circumstantial evidence for a common autoimmune etiology, namely lymphocytic hypophysitis, but we cannot deny the possibility that isolated ACTH deficiency could merely be masked by the previous steroid therapy for uveitis.

Pituitary autoantibodies were negative in our patient. The role of these antibodies in the pathogenesis of lymphocytic hypophysitis remains a matter of debate. Among 10 cases of lymphocytic hypophysitis, pituitary antibodies were detected in only 2 cases by various assays [6]. Pituitary antibodies have also been demonstrated in normal postpartum women, in patients with empty sella syndrome, and in some patients with pituitary tumors [7, 8]. The role of humoral immunity remains unclear.

PGA syndrome has been divided into two distinct types [9]. Type I PGA consists of at least two of the triad of Addison’s disease, hypoparathyroidism and chronic mucocutaneous candidiasis. Associated autoimmune disorders may also be present. Type II PGA commonly consists of Addison’s disease with chronic autoimmune thyroiditis, insulin-dependent diabetes mellitus, but no hypoparathyroidism or candidiasis. As this patient did not have Addison’s disease, she was classified as type III PGA, consisting of autoimmune thyroid disease, without Addison’s disease but with another autoimmune disease [9].

To our knowledge there have been only two reports on simultaneously found isolated ACTH deficiency and thyroid dysfunction. Kanemaru et al. [10] reported a case of isolated ACTH deficiency associated with transient thyrotoxicosis, hyperprolactinemia and liver dysfunction. In their case, both thyroid and liver functions normalized with glucocorticoid replacement therapy, but in our case spontaneously; and thyroid open biopsy did not show any evidence of autoimmune thyroiditis. Bevan et al. [11] described a female patient with isolated ACTH deficiency due to probable autoimmune hypophysitis associated with
postpartum thyroiditis. The clinical course of the patient described here is similar to that of the previously reported case, except for the postpartum relationship. Several previous studies have described a relationship between a decrease in the serum glucocorticoid level and painless thyroiditis (1, 12–15). For example, painless thyroiditis may occur after cessation of steroid therapy in patients with rheumatoid arthritis (1), after a unilateral adrenalectomy in patients with Cushing's syndrome (12–14), or after hypopituitarism following pituitary apoplexy (15). Exogenous or endogenous glucocorticoid is known to have immunosuppressive effects (16). The trigger of simultaneous occurrence of polyglandular failure in our case therefore seems to be a rebound rise in immune activity after cessation of prednisolone administration. Another point to consider carefully is the fact that recovery from the isolated ACTH deficiency was delayed by six months compared to the recovery of liver dysfunction or the hypothyroid state. The reason for this phenomenon is not yet clear. The time required for the restoration may differ according to the organs damaged.

In conclusion, we report the case of a woman who developed transient hypothyroidism due to Hashimoto's thyroiditis, autoimmune hepatitis, and isolated ACTH deficiency due to probable autoimmune hypophysitis at least two months after cessation of glucocorticoid treatment.

References


