Cushing Syndrome Uncovered During Treatment of Hyperthyroidism

Somnath Ghosh, MD, MS, and David H. Madoff, MD, PhD†*

Abstract: In this case report, we describe a patient in whom rather striking hypercortisolism became clinically apparent during the treatment of hyperthyroidism. The complex interplay between thyroid hormonogenesis and cortisol metabolism is discussed in depth as it pertains to the clinical presentation of this patient.

Key Words: Cushing syndrome, hyperthyroidism, glucocorticoid metabolism

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The complex hormonal interplay between the adrenal glands and the thyroid is well recognized.[1] Multiple case reports demonstrate the development of autoimmune thyroid disorders in predisposed patients upon treatment and resolution of hypercortisolism.[2–10] In contrast, in this case report we describe a patient who insidiously manifested the signs and symptoms of Cushing syndrome during treatment for hyperthyroidism.

CASE REPORT

A 48-year-old white female budget analyst with a 2-year history of palpitations was referred in March 2002 by her primary physician to evaluate an "overactive thyroid." She was well until 2 years prior, at which time she noticed occasional palpitations that she described as episodes of "heart racing," lasting about 30 seconds. These episodes were not associated with chest discomfort, lightheadedness, or syncope. She described poor sleep patterns, with frequent early-morning awakening. Also noted were occasional hand tremors and emotional irritability, without significant change in her weight. She experienced typical vasomotor symptoms of menopause, for which she was taking Premarin.

Her medical history was significant for neonatal jaundice, recent hemorrhoidectomy, and an uncomplicated pregnancy when she was 16 years old. There was no history of radiation exposure to her face and neck. Her medications included Premarin, calcium, and vitamin D supplements. She was allergic to penicillin, to which she developed an anaphylactic reaction 15 years ago. Her family history was significant for an unknown "thyroid condition" in her elder sister. She was born and raised in Baltimore, MD, and lives with her husband and son. She states that her job could be stressful at times. She had a 25-pack/year smoking history, having quit 8 years before. She consumes alcohol occasionally.

Physical examination revealed normal vital signs, dry skin, and a multinodular goiter about 50 g in weight. There was no lagophthalmos, globeophthalmos, signs of orbitopathy, thyroid acropachy, or pretibial myxedema. The cardiac examination was normal, and tendon reflexes were normal. The remainder of the examination was normal.

Laboratory tests showed an undetectable thyroid stimulating hormone (TSH) level, free T_4 1.4 ng/dL (nl 0.71–1.85), and total T_3 106 ng/dL (nl 60–161). No old thyroid studies were available. Radioactive iodine uptake was 44% at 24 hours (nl 25–35), and radionuclide scanning showed heterogeneous uptake, with multiple cold nodules in both lobes. Ultrasound-guided biopsy of 6 dominant nodules was negative for malignant cells and consistent with benign colloid nodules. Repeat thyroid function tests performed 2 months later were once again consistent with mild thyrotoxicosis due to a toxic multinodular goiter. Treatment options for her symptomatic thyrotoxicosis were discussed, including radioiodine ablation and antithyroid medications. In May 2002, the patient decided to start methimazole 5 mg daily.

In November 2002, she developed depressive symptoms. She decreased methimazole to 5 mg 4 times a week, since the free T_4 was 1.1 ng/dL and total T_3 was 56 ng/dL, at the lower end of the normal range. A few months later she had an episode of chest pain, with a normal evaluation, including a stress thallium study. Palpitations persisted and she was restarted on a daily dose of 5 mg methimazole. It is interesting to note that her TSH remained undetectable until April 2004, when it was 0.32 μIu/mL. At that time, the free T_4 was 0.83 ng/dL and total T_3 was 99 ng/dL. She denied any thyrotoxic symptoms thereafter.

In December 2003, she presented with a 7-pound weight gain and unexplained facial fullness. In addition, she complained of low energy and easy bruising. In contrast to her previously low blood pressure, her present blood pressure was labile and reached a documented maximum of 180/120 mm Hg. During this time, her free T_4 and total T_3 levels were normal; however, her TSH remained persistently suppressed. Methimazole was increased to 10 mg daily. Laboratory stud-

From the *Department of Medicine, Good Samaritan Hospital, Baltimore, MD; and †The Woodholme Center for Diabetes and Endocrine Disorders, Pikesville, MD.

Reprints: David H. Madoff, MD, PhD, The Woodholme Center for Diabetes and Endocrine Disorders, 1838 Greene Tree Road, Suite 120, Pikesville, MD 21208. E-mail: Birdjazz77@comcast.net.

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ies revealed unprovoked hypokalemia in the absence of hyperaldosteronism. The patient denied exogenous glucocorticoid exposure from any source. To address the possibility of Cushing syndrome, an overnight 1-mg dexamethasone suppression test was performed. The resultant 8 AM serum cortisol was 22.2 μg/dL (nl ≤1.8 μg/dL), and the concomitant salivary cortisol was 3.77 μg/dL (nl 0.18–0.95). Her 24-hour urine free cortisol was 171 μg (nl <105 μg). A morning adrenocorticotropic hormone (ACTH) level was undetectable, and the corresponding morning cortisol was 21.1 μg/dL. A CT scan performed in March 2004 revealed a benign-appearing 2.7-cm left adrenal tumor as the likely source of her ACTH-independent Cushing syndrome. Shortly thereafter, a laparoscopic left adrenalectomy was performed, without complications. The pathology was consistent with a benign cortisol-producing adrenal adenoma.

Postoperatively she received an adequate replacement dose of prednisone in anticipation of adrenal insufficiency due to chronic preoperative suppression of the hypothalamic-pituitary-adrenal axis. An ACTH-stimulation test performed 1 week after surgery confirmed a markedly blunted cortisol response to intravenous cosyntropin. Despite adequate glucocorticoid therapy, she had an episode consistent with mild adrenal crisis 3 weeks after the adrenalectomy and required hospitalization. Glucocorticoid replacement therapy was gradually weaned and discontinued over the next year. The patient returned to her usual state of health.

DISCUSSION

Our patient was initially treated for hyperthyroidism with methimazole. She subsequently developed significant Cushing-like features and hypercortisolism while on antithyroid therapy. Laparoscopic surgery revealed a 2.7-cm cortisol-producing left adrenal adenoma causing ACTH-independent Cushing syndrome. This, to our knowledge, is the first documented case of Cushing syndrome diagnosed during treatment for thyrotoxicosis.

There have been many reports of exacerbation of Graves disease and other autoimmune thyroid diseases following unilateral adrenalectomy for Cushing syndrome.[2–10] The pathophysiology in these cases is thought to be glucocorticoid-dependent suppression of latent autoimmune thyrotoxicosis, with the development of overt thyroid disease after the abrupt reduction of plasma glucocorticoid levels following adrenalectomy. This sequence of events is reversed in our patient, and the pathophysiology is quite different.

In all likelihood, the adrenal adenoma was present and metabolically active for years, yet she did not manifest the signs and symptoms of Cushing syndrome until her hyperthyroidism was treated. There are at least 3 possible explanations for this clinical scenario. First, treatment of thyrotoxicosis and expression of latent Cushing syndrome could be 2 chance events. We find this possibility highly improbable since the secretory pattern of her adrenal adenoma would not likely have changed substantially over the 20 months during which she was treated with methimazole. Our patient clearly had an abrupt and fairly defined onset of the Cushingoid phenotype. Second, mild chronic thyrotoxicosis could have suppressed the Cushingoid phenotype, and treatment of her thyrotoxicosis allowed for full-blown expression of Cushing syndrome. Third, it is possible that longstanding, mild thyrotoxicosis resulted in chronic cortisol hypersecretion and autonomous growth of the left adrenal gland. The latter 2 possible explanations are not mutually exclusive. We will discuss these 2 possibilities.

In 1958, Peterson[11] demonstrated significantly increased cortisol production and clearance rates in a group of thyrotoxic patients. Treatment of hyperthyroidism in these subjects returned cortisol metabolism to normal. McGuire and Tomkins[12] showed that the hyperthyroid state increased cortisol degradation by enhancing the activity of hepatic δ-4,5-α-reductase and δ-4,5-β-reductase. In 1961, Hellman et al[13] showed enhanced conversion of metabolically active cortisol to the inactive metabolite cortisone via the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) in thyrotoxic human subjects. By inactivating cortisol, overexpression of 11β-HSD would serve to buffer the thyrotoxic patient from the effects of cortisol overproduction at the level of the glucocorticoid receptor.[14] Plasma cortisol levels are normal in hyperthyroid patients despite elevated production rates and enhanced inactivation to cortisone. As a result, the total daily renal excretion of 17 hydroxy-corticoids is increased.[15,16] In summary, in the thyrotoxic state the adrenal glands chronically increase glucocorticoid production to maintain normal serum cortisol levels in the presence of enhanced cortisol catabolism.[17] Indeed, secretion of adrenocorticotropic hormone (ACTH) has been reported to be elevated in the face of hyperthyroidism[18], and bilateral adrenal hypertrophy has been demonstrated in animals experimentally rendered hyperthyroid.[11]

For many years, our patient most certainly had a small cortisol-producing adrenal adenoma and subclinical Cushing syndrome. The subsequent development of mild thyrotoxicosis due to a toxic multinodular goiter resulted in increased catabolism of cortisol and relative hypersecretion of ACTH via the mechanisms described above. The thyrotoxic state could well have accelerated ACTH-mediated growth of her adrenal adenoma. At the same time, hyperthyroidism could have suppressed the expression of Cushing syndrome by maintaining relatively normal cortisol levels. Once the patient's thyrotoxicosis was treated with methimazole, hypercortisolism became clinically evident and the adrenal adenoma was discovered. Cushing syndrome resolved entirely following laparoscopic adrenalectomy.

CONCLUSION

This case report illustrates the complex interplay between thyroid hormonogenesis and cortisol metabolism. A patient was described in which rather striking hypercortisolism became clinically apparent during the treatment of hyperthyroidism. Based on the principles described herein, we suggest that clinicians consider the effects of thyroid hormone on cortisol metabolism, as well as the effects of cortisol on autoimmune thyroid disease. Several clinical scenarios have been described in the literature. First, resolving hyperthyroidism could expose underlying glucocorticoid excess as described in this case report. Second, treating hypo-

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thyroidism in a patient with limited adrenal function could precipitate adrenal insufficiency. Third, glucocorticoid therapy in patients with adrenal insufficiency could mask autoimmune thyroid disease. Last, the treatment of hypercortisolism could trigger underlying autoimmune thyroid disease.

Based upon our reported experience, we recommend that physicians observe patients for signs and symptoms of Cushing syndrome during the treatment of hyperthyroidism.

REFERENCES

1. Niepomniszcze H, Pitoia F, Katz SB, et al. Primary thyroid disorders in endogenous Cushing's syndrome. *Eur J Endocrinol*. 2002;147:305–311.
2. Pishdad GR. Cushing's syndrome as a manifestation of hypothyroidism. *Clin Endocrinol (Oxf)*. 2004;60:271.
3. Takasu N, Komiya I, Nagasawa Y, et al. Exacerbation of autoimmune thyroid dysfunction after unilateral adrenalectomy in patients with Cushing's syndrome due to an adrenocortical adenoma. *N Engl J Med*. 1990;322:1708–1712.
4. Arikan E, Guldiken S, Altun BU, et al. Exacerbations of Graves' disease after unilateral adrenalectomy for Cushing's syndrome. *J Endocrinol Invest*. 2004;27:574–576.
5. Morita H, Isaji M, Mune T, et al. Transient Graves disease developing after surgery for Cushing disease. *Am J Med Sci*. 2002;323:162–165.
6. Haraguchi K, Hiramatsu K, Onaya T. Transient thyrotoxicosis after unilateral adrenalectomy in two patients with Cushing's syndrome. *Endocrinol Jpn*. 1984;31:577–582.
7. Takasu N, Ohara N, Yamada T, et al. Development of autoimmune thyroid dysfunction after bilateral adrenalectomy in a patient with Carney's complex and after removal of ACTH-producing pituitary adenoma in a patient with Cushing's disease. *J Endocrinol Invest*. 1993;16:697–702.
8. Romano A, Blethen SL. Subacute thyroiditis presenting as Cushing's syndrome: case report. *Horm Res*. 1991;35:170–172.
9. Colao A, Pivonello R, Faggiano A, et al. Increased prevalence of thyroid autoimmunity in patients successfully treated for Cushing's disease. *Clin Endocrinol (Oxf)*. 2000;53:13–9.
10. Cioni K, Pantaleoni M, Toschi E, et al. [Exacerbation of autoimmune hypothyroidism after hemi-hypophysehysectomy in a patient with Cushing's disease]. *Minerva Endocrinol* 1993;18:139–141.
11. Peterson RE. The influence of the thyroid on adrenal cortical function. *J Clin Invest.* 1958;37:736.
12. McGuire JS, Tomkins GM. The effects of thyroxine administration on the enzymic reduction of delta-4-5-ketosteroids. *J Biol Chem.* 1959;234:791.
13. Hellman L, Bradlow HL, Zumoff B, et al. Influence of thyroid hormone on hydrocortisone production and metabolism. *J Clin Endocrinol Metab*. 1961;21:1231–1247.
14. Tomlinson JW, Walker EA, Bujalska IJ, et al. 11β-Hydroxysteroid dehydrogenase type 1: a tissue-specific regulator of glucocorticoid response. *Endocr Rev*. 2004;25:831–866.
15. Kenny FM, Iturzaeta N, Preeyasombat C, et al. Cortisol production rate, VII: hypothyroidism and hyperthyroidism in infants and children. *J Clin Endocrinol*. 1967;27:1616.
16. Bray GA, Jacobs HS. Thyroid activity and other endocrine glands. In: *Handbook of Physiology, Endocrinology*.Washington, DC: American Physiology Society; 1974:413.
17. Gallagher TF, Hellman L, Finkelstein J, et al. Hyperthyroidism and cortisol secretion in man. *J Clin Endocrinol Metab.* 1972;34:919.
18. Hilton JG, Black WC, Athos W, et al. Increased ACTH-like activity in plasma of patients with thyrotoxicosis. *J Clin Endocrinol Metab.* 1962;22:900.

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