Development of Hyperthyroidism Following Primary Hypothyroidism: A Case Report

Yueh-Hua Chung, Horng-Yih Ou, and Ta-Jen Wu
Division of Endocrinology and Metabolism, Department of Internal Medicine,
National Cheng Kung University Hospital, Tainan, Taiwan.

Development of hyperthyroidism following primary hypothyroidism is uncommon, and only a few documented cases have been reported. Alterations in thyroid-stimulating hormone receptor antibodies in serum are currently considered to play the main role in the pathophysiology, but the exact mechanism is still unknown. Here, we report the case of a 60-year-old man with disturbed consciousness due to hyponatremia. Thyroid function tests showed primary hypothyroidism with a high anti-microsomal antibody titer (1:6,400). The patient experienced weight loss and exophthalmos 6 years later. Serum thyroid hormone levels were increased and thyroxine treatment was discontinued, but the patient remained thyrotoxic 2 months later. ^{131}I thyroid uptake was 40.9% at 24 hours, and bilateral thyroid lobes were not enlarged with diffuse radioactivity. Six months later, the patient was still thyrotoxic and therapy with methimazole 10 mg/day was started. He is now taking methimazole and is euthyroid.

Key Words: hyperthyroidism, hypothyroidism, Graves' disease
(*Kaohsiung J Med Sci* 2004;20:188–91)

Hypothyroidism following Graves' hyperthyroidism spontaneously or after anti-thyroid drug treatment is well known, and is believed to be due to destruction of the thyroid gland [1] or the appearance of blocking thyroid-stimulating hormone (TSH) receptor antibodies [2]. However, the development of hyperthyroidism following primary hypothyroidism is uncommon and the mechanism of this phenomenon is unknown. We present a patient who developed hyperthyroidism following primary hypothyroidism, and review similar cases in the medical literature.

Case Presentation

In March 1992, a 60-year-old male presented to our institution for consciousness disturbance. He had no history of serious illnesses, thyroid diseases, surgery or drug consumption. Hyponatremia (113 mmol/L) was noted, so thyroid function was tested. A diagnosis of primary hypothyroidism was made on the basis of low serum thyroxine (T4) (1.1 μg/dL) and triiodothyronine (T3) (32.6 ng/dL), and high TSH (153.429 μU/mL) and positive microsomal antibody (1:6,400). He did not have exophthalmos and the thyroid gland was not palpable. ^{131}I thyroid uptake in April 1992 was 1.7% (4–12%) at 2 hours and 0.78% (15–40%) at 24 hours; both thyroid lobes were hardly visible on scintigraphy due to the very low uptake of radioiodine. After treatment with T4, the clinical manifestation regressed and thyroid hormone levels became normal. The patient was treated with T4 200 mg/day and regularly followed at the outpatient clinic, where he had normal serum T4 (7.4–10.4 μg/dL) and mildly elevated serum TSH (6.562–14.061 μU/mL).

In February 1998, the patient presented with weight loss. Serum T4 concentration was 13.9 μg/dL, T3 was 240.7 ng/dL and TSH was 0.024 μU/mL. He had mild exophthalmos without soft-tissue, extraocular-muscle or corneal involvement. Goiter size did not increase. T4 therapy was tapered and discontinued by September 1998. After withdrawal of T4 therapy, ^{131}I thyroid uptake in November

Received: June 20, 2003 Accepted: December 12, 2003
Address correspondence and reprint requests to: Dr. Ta-Jen Wu, Division of Endocrinology and Metabolism, Department of Internal Medicine, National Cheng Kung University Hospital, 138 Sheng-Li Road, Tainan 704, Taiwan.
E-mail: djwu@mail.ncku.edu.tw

1998 was 1.31% at 2 hours and 40.9% at 24 hours; scintigraphy showed that the bilateral thyroid lobes were not enlarged with diffuse radioactivity.

Six months later, the patient was still thyrotoxic, with elevated serum T4 and T3 concentrations, and therapy with methimazole 10 mg/day was started. He became euthyroid after the start of methimazole therapy. In May 2002, he redeveloped hypothyroidism, with low serum T4 (1.5 μg/dL) and high TSH (178.43 μU/mL) concentrations, when the methimazole dose was titrated from 20 to 30 mg/day. After the methimazole dosage was decreased to 15 mg/day, he became euthyroid and remained so until the time of writing. His clinical course, laboratory findings and changes in thyroid-related antibodies are shown in the Figure and Table.

Discussion

The diagnosis of primary hypothyroidism in this patient was well founded, as shown by hyponatremia with low serum T4 and high serum TSH levels. The presence of a high anti-microsomal antibody titer favors the possibility of autoimmune thyroiditis. The possibility of subacute thyroiditis, silent thyroiditis or drug-induced hypothyroidism was very low according to the patient's clinical course and laboratory findings. After the development of hyperthyroidism, the possibility of transient thyrotoxicosis due to destructive thyroiditis can be excluded, especially when ^{131}I thyroid uptake is not low.

Development of hyperthyroidism following primary hypothyroidism is a rare phenomenon and only a few documented cases have been reported [3–7]. Primary hypothyroidism was traditionally thought to result from thyroid destruction. Hence, it is amazing that a patient with primary hypothyroidism subsequently develops hyperthyroidism. It has been postulated that hypothyroidism previous to hyperthyroidism may be due to TSH receptor blocking antibodies, causing reversible hypothyroidism. The change in the properties of TSH receptor antibodies from blocking to stimulating results in development of hyperthyroidism after primary hypothyroidism.

TSH receptor antibodies have been reported in about 10% of patients with atrophic autoimmune thyroiditis and in about 20% of patients with goiterous autoimmune thyroiditis [8,9]. Takasu et al reported the disappearance of TSH receptor blocking antibodies and spontaneous recovery from hypothyroidism in 5% to 10% of patients with chronic autoimmune thyroiditis [9]. If TSH receptor antibodies change from blocking to stimulating in patients with reversible primary hypothyroidism, these patients will develop hyperthyroidism after primary hypothyroidism.

There are only 36 cases of hyperthyroidism following primary hypothyroidism in the literature. Only three cases documented alterations in TSH receptor antibodies from blocking to stimulating [5–7]. As TSH receptor antibodies

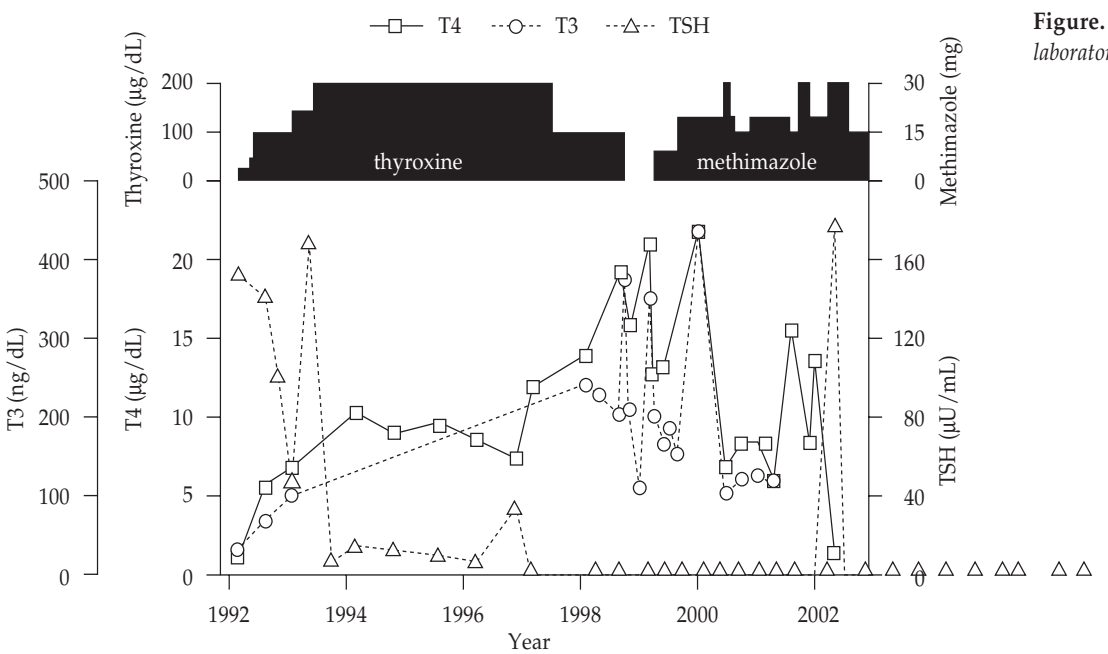

Figure. *Clinical course and laboratory findings.*

Table. Changes in thyroid related antibodies

Date	T4 (μg/dL)/TSH (μU/mL)	Goiter	Exophthalmos	ATA (< × 100)	AmiA (< × 100)	TBII (%) (< 15)
April 1992	1.1 /153.429	No	No	× 100	× 6,400	ND
August 1996	8.6 /6.562	No	No	× 100	× 1,638,400	ND
November 1998	15.9 /0.02	No	Yes	× 100	× 25,600	ND
February 2003	9.9 /0.02	No	Yes	ND	ND	56

T4 = thyroxine; TSH = thyroid-stimulating hormone; ATA = anti-thyroglobulin antibody; AmiA = anti-microsomal antibody; TBII = TSH-binding inhibitory immunoglobulin; ND = not done.

were not detected during hypothyroidism in many of the other cases, it is very difficult to explain the cause of reversible hypothyroidism. This phenomenon is currently considered to be due to alterations in TSH receptor antibodies in the serum of some patients, but the exact mechanism remains unknown.

Our patient developed hypothyroidism during titration of methimazole therapy in May 2002. It has been suggested that patients such as these are very sensitive to anti-thyroid drugs and easily develop hypothyroidism. The same phenomenon was noted among three cases reported by Takasu et al [7].

In conclusion, our patient developed hyperthyroidism 6 years after being diagnosed with primary hypothyroidism. Although it is a rare phenomenon, we should keep in mind that primary hypothyroidism due to autoimmune thyroiditis is not always a persistent state, and that hyperthyroidism may develop in some patients.

References

1. Irvine WJ, Gray RS, Toft AD, et al. Spectrum of thyroid function in patients remaining in remission after antithyroid drug therapy for thyrotoxicosis. *Lancet* 1977;ii:179–81.
2. Kasagi K, Iida Y, Konishi J, et al. Paired determination of thyroid-stimulating and TSH-binding inhibitory activities in patients with Graves' disease during antithyroid drug treatment. *Acta Endocrinol* 1986;111:474–80.
3. Bell PM, Sinnamon DG, Smyth PP, et al. Hyperthyroidism following primary hypothyroidism in association with polyendocrine autoimmunity. *Acta Endocrinol* 1985;108:491–7.
4. Kasagi K, Konishi J, Iida Y, et al. Changes in thyroid stimulating and TSH-binding inhibitory activities in a patient who developed hyperthyroidism due to Graves' disease following primary hypothyroidism. *Clin Endocrinol* 1986;25:519–25.
5. Takeda K, Takamatsu J, Kasagi K, et al. Development of hyperthyroidism following primary hypothyroidism: a case report with changes in thyroid-related antibodies. *Clin Endocrinol* 1988;28:341–4.
6. Cho BY, Shong YK, Lee HK, et al. Graves' hyperthyroidism following primary hypothyroidism: sequential changes in various activities of thyrotropin receptor antibodies. *Acta Endocrinol* 1989;120:447–50.
7. Takasu N, Yamada T, Sato A, et al. Graves' disease following hypothyroidism due to Hashimoto's disease: studies of eight cases. *Clin Endocrinol* 1990;33:687–98.
8. Tamaki H, Amino N, Kimura M, et al. Low prevalence of thyrotropin receptor antibody in primary hypothyroidism in Japan. *J Clin Endocrinol Metab* 1990;71:1382–6.
9. Takasu N, Yamada T, Takasu M, et al. Disappearance of thyrotropin-blocking antibodies and spontaneous recovery from hypothyroidism in autoimmune thyroiditis. *N Engl J Med* 1992;326:513–8.

原發性甲狀腺低下轉變為甲狀腺亢進 — 病例報告

鍾岳樺　歐弘毅　吳達仁

國立成功大學 附設醫院內科部 內分泌新陳代謝科

原發性甲狀腺低下轉變為甲狀腺亢進是相當罕見的現象，而且回顧文獻也只有少數診斷確定的案例報告。目前認為其病理機轉是因為甲促素受體抗體轉變所引起，但是真正的原因目前仍然不明。我們報告一個病例，病人是一名六十歲男性，因為低血鈉而導致意識不清，所以進一步接受甲狀腺功能檢驗而被診斷有原發性甲狀腺低下並接受甲狀腺素治療。但是在六年後病人開始出現體重減輕以及凸眼的症狀，甲狀腺功能檢驗顯示為甲狀腺亢進。但是即使在停止甲狀腺素治療後兩個月所做的甲狀腺功能檢驗依然是甲狀腺亢進，同時所做的碘 131 甲狀腺掃描為兩側廣泛性顯影，且 24 小時攝取率為 40.9%。經過六個月的追蹤後，病人仍然是甲狀腺亢進，所以他開始接受抗甲狀腺藥物治療，目前甲狀腺功能控制在正常範圍內。

關鍵詞：甲狀腺低下，甲狀腺亢進，葛瑞夫茲氏病

（高雄醫誌 2004;20:188–91）

收文日期：92 年 6 月 20 日
接受刊載：92 年 12 月 12 日
抽印本索取處：吳達仁醫師
國立成功大學 附設醫院內科部 內分泌新陳代謝科
台南市勝利路 138 號