# Widely metastatic follicular thyroid cancer may cause $T_3$ thyrotoxicosis from increased tumor deiodinase activity identifiable only by serum $T_3$ levels and stopping levothyroxine therapy

Miyauchi A, Takamura Y, Ito Y, Miya A, Kobayashi K, Matsuzuka F, Amino N, Toyoda N, Nomura E, Nishikawa M. 3,5,3´-Triiodothyronine thyrotoxicosis due to increased conversion of administered levothyroxine in patients with massive metastatic follicular thyroid carcinoma. J Clin Endocrinol Metab 2008;93:2239-42.

## SUMMARY

**BACKGROUND** Patients with widely metastatic thyroid cancer may have triiodothyronine ($T_3$) thyrotoxicosis due to increased deiodinase-1 and deiodinase-2 (D-1 and D-2) activity that converts thyroxine ($T_4$) to $T_3$ in amounts sufficient to cause thyrotoxicosis, but the prevalence, diagnosis, and treatment of this problem have not been fully elucidated. This retrospective study describes the prevalence and cause of $T_3$ thyrotoxicosis in this setting and describes the clues to its diagnosis.

**METHODS** The study subjects were 58 patients with metastatic thyroid cancer measuring 2 cm or larger in diameter; 31 (54%) had papillary cancer, 20 (35%) had follicular cancer, and 7 (12%) had medullary thyroid cancer. In all, there were 79 metastatic sites, 42 (53%) in the lung, 23 (29%) in bone (29%), 4 (5%) in the liver, and 10 (13%) in other sites. Study controls were 17 patients with papillary thyroid cancer who had no sign of tumor recurrence after total thyroidectomy. Sera from all patients were obtained for measurements of thyrotropin (TSH), free $T_4$ ($FT_4$), free $T_3$ ($FT_3$), and thyroglobulin (Tg). Frozen stored sera remaining from past measurements were used to measure $FT_3$ to clarify the course of change in these patients. Three stored frozen tumors, two primary tumors and one metastatic subcutaneous tumor from two patients were studied for measurement of D-1 and D-2 activity.

**RESULTS** Four of 20 (20%) patients had $T_3$ thyrotoxicosis; their mean (±SD) age was 59.5±16.1 years. There were no statistical differences in the mean age, in levels of TSH and $FT_4$ among the four study groups with papillary, follicular, and medullary thyroid cancer, and in the control patients with papillary cancer (Figure 1). Patients with papillary or follicular thyroid cancer were taking significantly larger doses of levothryoxine (L-$T_4$) than the other groups ($P<0.05$; Figure 1) The four patients with $T_3$ thyrotoxicosis and follicular cancer had abnormally high serum $FT_3$ levels and a serum $FT_3/FT_4$ ratio greater than 3.5 (Figure 2). Two patients with $T_3$ thyrotoxicosis had palpitations, tachycardia, and weight loss, while the others had only mild tachycardia. Withdrawal of L-$T_4$ in the four patients with thyrotoxicosis for 1 week resulted in a decrease of serum $FT_4$ and $FT_3$ levels in all four patients, indicating that the high $T_3$ levels were not produced by functioning metastases but instead originated from increased conversion of $T_4$ to $T_3$ in tumor tissue.

Normal thyroid tissue D-1 and D-2 activities, respectively, were 140±112 pmol/mg of tumor protein /hr, and 8.6±8.6

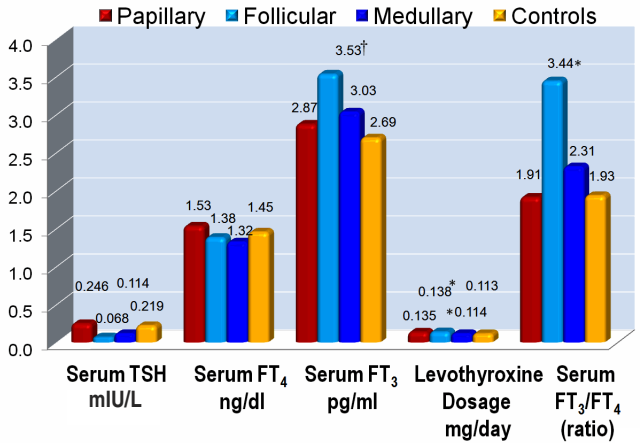


Figure 1. Serum thyroid-function tests and levothyroxine dosage in patients with papillary, follicular, and medullary thyroid cancer. Normal values are as follows: TSH, 0.3 to 4 mIU/L; $FT_4$, 0.7 to 1.6 ng/dl; and $FT_3$, 1.7 to 3.7 pg/ml. †$P<0.001$ comparing papillary cancer with and without recurrence vs. follicular cancer. *$P<0.05$ comparing papillary and follicular cancer with medullary cancer and tumors without recurrences.

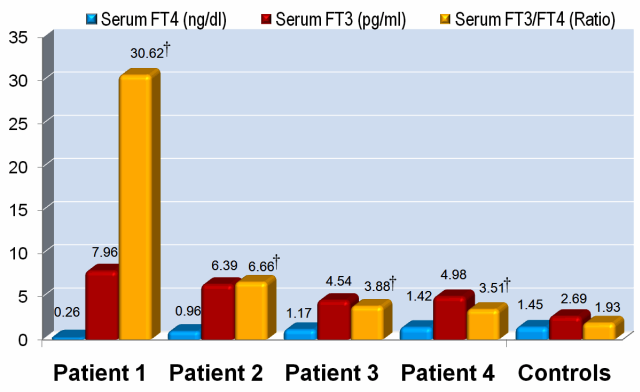


Figure 2. Thyroid-function tests are shown in four patients and contr showing the importance of serum $FT_3$ and $FT_3/FT_4$ ratios. †$P<0.001$ for patients vs. controls.

fmol/mg of tumor protein/hr. In contrast, tumor tissues from patients with $T_3$ thyrotoxicosis had D-1 and D-2 activities that were, respectively, about 8-fold and 250-fold those in normal thyroid tissues.

Analyses of stored sera from two patients with $T_3$ thyrotoxicosis revealed that $FT_3$ levels had started to increase about 2 to 4 years earlier while $FT_4$ levels gradually declined but remained in the normal range. Also, in one patient both $FT_4$ and $FT_3$ declined to undetectable levels during a 1-month period in which L-$T_4$ was stopped to facilitate $^{131}I$ therapy.

**CONCLUSION** One in five patients with widely metastatic follicular thyroid cancer has $T_3$ thyrotoxicosis from increased tumor deiodinase activity that can be identified by measuring serum $T_3$ levels and stopping levothyroxine therapy.

## COMMENTARY

Approximately 80% of serum $T_3$ is formed by outer-ring deiodination of $T_4$ removing either iodine atom from the outer ring (designated as 5´ deiodination), which occurs in various tissues. This deiodination is catalyzed by iodothyronine D-1 mainly expressed in the liver, kidney, and thyroid gland and D-2, mainly expressed in the brain, pituitary, cardiac and skeletal muscle, and placenta. Thus, converting it to 3,5,3´ $T_3$. Deiodinase-3 (D-3), which is found in the brain, skin, and placenta catalyzes the removal of one iodine atom in the inner ring of $T_4$ or $T_3$ to form 3,3, 5´ triiodothyronine, reverse $T_3$, thus inactivating both hormones. Studies have shown that D2 expression in human thyroid gland is regulated at the transcriptional level through the TSH receptor and is elevated in patients with Graves' disease and in hyperfunctioning thyroid adenoma (1).

Routine surveillance of patients with differentiated thyroid cancer usually includes measurements of serum TSH, $T_4$ or $FT_4$ and serum thyroglobulin levels; however, serum $T_3$ measurements are not performed routinely. The only obvious reason to do this is the appearance of thyrotoxicosis without an elevation of serum $FT_4$

Kim et al. (2) first identified three patients with large or widely metastatic follicular thyroid cancer who had persistently increased $T_3/T_4$ ratios in the absence of $T_3$ production by the tumor. They assayed D-1 and D-2 activity in a large follicular thyroid cancer resected from one of these patients and found that D-2 was 8-fold higher than in normal human thyroid tissue and resection of the tumor, leaving the left thyroid lobe intact, normalized the serum $T_3/T_4$ ratio. They concluded that this had probably come about by the increase in D-2 activity.

The study by Miyauchi et al. adds important information concerning $T_3$ thyrotoxicosis in patients with follicular thyroid cancer. Miyauchi and colleagues (3) previously studied two cases of follicular thyroid cancer with distant metastases that showed high levels of $FT_3$ with $FT_4$ levels in the low normal range. They found that both D-1 and D-2 were expressed in the primary tumor and lung metastases at the same level as in normal thyroid tissue, and they suggested that $T_3$ toxicosis was caused by $T_4$ hyperconversion of administered L-$T_4$.

The present study adds more weight to these observations. Three of the four patients with high $FT_3$ levels had normal $FT_4$ levels, while one had clearly low $FT_4$ levels. Retrospective measurements of $FT_3$ in the previously stored frozen sera samples indicated that an increase in serum $FT_3$ levels above the upper normal range had occurred well before the present study. The authors point out that low serum $T_4$ levels in patients being treated with a fixed dose of levothyroxine can be a clue to the early diagnosis of this problem. Moreover, withdrawal of levothyroxine for 1 week resulting in a fall in serum $FT_4$ and $FT_3$ is an easy way to rule out the possibility of $T_3$ production by a functioning tumor. Of considerable importance, only two patients had mild symptoms of thyrotoxicosis such as palpitations and weight loss; these were common symptoms in patients with advanced cancer and the clinical signs were even vaguer.

It is important to recognize this syndrome by measuring serum $T_3$ levels to avoid unnecessarily increasing the L-$T_4$ dosage that might promote severe thyrotoxicosis.

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### References


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