HYPERTHYROIDISM

Widely metastatic follicular thyroid cancer may cause T₃ thyrotoxicosis from increased tumor deiodinase activity identifiable only by serum T₃ levels and stopping levothyroxine therapy


SUMMARY

BACKGROUND Patients with widely metastatic thyroid cancer may have triiodothyronine (T₃) thyrotoxicosis due to increased deiodinase-1 and deiodinase-2 (D-1 and D-2) activity that converts thyroxine (T₄) to T₃ 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 T₃ 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 T₄ (FT₄), free T₃ (FT₃), and thyroglobulin (Tg). Frozen stored sera remaining from past measurements were used to measure FT₃ 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 T₃ 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 FT₄ 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 levothyroxine (L-T₄) than the other groups (P<0.05; Figure 1). The four patients with T₃ thyrotoxicosis had abnormally high serum FT₃ levels and a serum FT₃/FT₄ ratio greater than 3.5 (Figure 2). Two patients with T₃ thyrotoxicosis had palpitations, tachycardia, and weight loss, while the others had only mild tachycardia. Withdrawal of L-T₄ in the four patients with thyrotoxicosis for 1 week resulted in a decrease of serum FT₄ and FT₃ levels in all four patients, indicating that the high T₃ levels were not produced by functioning metastases but instead originated from increased conversion of T₄ to T₃ 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 four study groups showing the importance of serum FT₃ and FT₃/FT₄ ratios. †P<0.001 for patients vs. controls.](image1)

![Figure 2. Thyroid-function tests are shown in four patients and controls showing the importance of serum FT₃ and FT₃/FT₄ ratios. †P<0.001 for patients vs. controls.](image2)
fmol/mg of tumor protein/hr. In contrast, tumor tissues from patients with T3 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 T3 thyrotoxicosis revealed that FT3 levels had started to increase about 2 to 4 years earlier while FT4 levels gradually declined but remained in the normal range. Also, in one patient both FT4 and FT3 declined to undetectable levels during a 1-month period in which L-T4 was stopped to facilitate ¹³¹I therapy.

**CONCLUSION** One in five patients with widely metastatic follicular thyroid cancer has T3 thyrotoxicosis from increased tumor deiodinase activity that can be identified by measuring serum T3 levels and stopping levothyroxine therapy.

The study by Miyachi et al. adds important information concerning T3 thyrotoxicosis in patients with follicular thyroid cancer. Miyachi and colleagues (3) previously studied two cases of follicular thyroid cancer with distant metastases that showed high levels of FT3 with FT4 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 T3 toxicosis was caused by T4 hyperconversion of administered L-T4.

The present study adds more weight to these observations. Three of the four patients with high FT3 levels had normal FT4 levels, while one had clearly low FT4 levels. Retrospective measurements of FT3 in the previously stored frozen sera samples indicated that an increase in serum FT3 levels above the upper normal range had occurred well before the present study. The authors point out that low serum T4 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 FT4 and FT3 is an easy way to rule out the possibility of T3 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 T3 levels to avoid unnecessarily increasing the L-T4 dosage that might promote severe thyrotoxicosis.

**COMMENTARY**

Approximately 80% of serum T3 is formed by outer-ring deiodination of T4 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’-T3. 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 T4 or T3 to form 3,3,5’-triiodothyronine, reverse T3, 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, T3 or FT3 and serum thyroglobulin levels; however, serum T3 measurements are not performed routinely. The only obvious reason to do this is the appearance of thyrotoxicosis without an elevation of serum FT4.

Kim et al. (2) first identified three patients with large or widely metastatic follicular thyroid cancer who had persistently increased T3/T4 ratios in the absence of T3 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 T3/T4 ratio. They concluded that this had probably come about by the increase in D-2 activity.

References