

# High T3 Syndrome Associated with Metastatic Papillary and Poorly Differentiated Thyroid Cancer

Run Yu, MD, PhD

Division of Endocrinology, UCLA David Geffen School of Medicine, Los Angeles, CA.

runyu@mednet.ucla.edu

*\*Corresponding Author: Dr. Run Yu, MD, PhD, Division of Endocrinology, UCLA David Geffen School of Medicine, Los Angeles, CA.*

## Abstract

Circulating levels of free thyroxine (T4) and triiodothyronine (T3) are tightly regulated by thyrotropin (TSH) via deiodinases. Free T4 and T3 levels are usually congruent but may become discordant when deiodinase activities are altered by diseases or medications. High T3 syndrome is seen in hyperthyroidism, Allan-Herndon-Dudley syndrome, and massive metastatic follicular thyroid cancer (FTC), where the T4-to-T3 conversion is increased (1-3). High T3 syndrome has not been reported in metastatic papillary thyroid cancer (PTC) or poorly differentiated thyroid cancer (PDTC). Described here is the first case of high T3 syndrome in a patient with a large metastatic burden of PTC and PDTC.

## INTRODUCTION

Circulating levels of free thyroxine (T4) and triiodothyronine (T3) are tightly regulated by thyrotropin (TSH) via deiodinases (1). Free T4 and T3 levels are usually congruent but may become discordant when deiodinase activities are altered by diseases or medications. Low T3 syndrome is a well-known condition where the T4-to-T3 conversion is inhibited by critical illness; high T3 syndrome is seen in hyperthyroidism, Allan-Herndon-Dudley syndrome, and massive metastatic follicular thyroid cancer (FTC), where the T4-to-T3 conversion is increased (1-3). Described here is a case of high T3 syndrome in metastatic papillary and poorly differentiated thyroid cancer (PTC and PDTC).

## CASE REPORT

A 60-year-old male presented for treatment of metastatic thyroid cancer. At age 30, he was found to have a goiter by physical examination and was given levothyroxine (LT4) 25 mcg daily. At age 54, CT urogram (for hematuria) incidentally found a 1.8 cm expansile lytic lesion on the right 9th rib; bone scan showed high signal at the location; he did not follow up as recommended. At age 60, he felt 2 large masses, one on the back of head and the other on the right chest wall. The masses were biopsied and

their histology and immunochemical profile were consistent with metastatic PTC and PDTC, respectively. Thyroid ultrasound confirmed multinodular goiter. FDG PET/CT showed a large lytic lesion in occipital bone, 5.5 x 4.6 cm, a right lytic rib mass 7 x 9.5 cm, and numerous other lytic lesions in ribs, sternum, and right ischium. He underwent total thyroidectomy. Histologically, the left lobe contained a 1.9-cm PTC, follicular variant; the right lobe contained a 3.8-cm PDTC with a 20% component of follicular variant of PTC. Postoperatively, he started LT4 replacement (Table 1). A few days after thyroidectomy, the patient developed aspiration pneumonia, cardiac arrest, pleural effusions, and acute kidney injury. He was intubated and required tracheostomy, percutaneous endoscopic gastrostomy, and thoracentesis. He stayed in ICU for 3 weeks. His condition gradually improved and 4 weeks after thyroidectomy, he was discharged with tracheostomy and gastrostomy tubes. His conditions continued to improve; the tracheostomy and gastrostomy tubes were removed several months after discharge. One year after thyroidectomy, he received radioactive iodine ablation (RAI). Post-RAI scan showed iodine-avid lymph nodes in the anterior cervical and supraclavicular regions and multiple chest wall soft tissue lesions with low iodine avidity.

Only after RAI, did it become evident that his thyroid

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function test results were very unusual (Table 1). For example, 1 month after RAI, while taking LT4 100 mcg daily, his TSH level was 3.5 mIU/L (normal 0.3-4.7) and free T4 0.6 ng/dL (0.8-1.6); 3 months after RAI, TSH was 0.21 mIU/L and free T4 0.7 ng/dL. He never took liothyronine and he appeared grossly healthy after RAI; the post-RAI scan did not show brain up take. Thyrotroph deficiency was deemed very unlikely; abnormal metabolism of LT4 was suspected. Free T3 and reverse T3 were measured in the same blood specimen drawn 3 months after RAI and free T3 was elevated while reverse T3 suppressed (Table1).

In retrospect, nearly 5 months before thyroidectomy, free T4 was already low with concomitant high normal free T3 and normal TSH. Before thyroidectomy, free T4 index was also low while he was clinically euthyroid. He was ultimately diagnosed with high T3 syndrome associated with metastatic thyroid cancer. His thyroid function test results during ICU stay were probably due to 3 concurrent conditions: high T3 syndrome, low T3 syndrome, and poor LT4 absorption. Because high T3 syndrome was not recognized when he was in ICU, the LT4 dose was increased, resulting in complete suppression of TSH (Table 1)

	141 days <i>before</i> total thyroidectomy	6 days <i>before</i> total thyroidectomy	23 days after total thyroidectomy (in ICU, after cardiac arrest, pleural effsuion, and tracheostomy)	52 days after total thyroidectomy (3 days after discharge in stable condition)	398 days after total thyroidectomy, 33 days afetr RAI	459 days after total thyroidectomy, 94 days after RAI
Daily thyroid replacement	LT4, 25 mcg, orally	LT4, 25 mcg, orally	LT4, 137 mcg, per nasogastric tube	LT4, 175 mcg, per gastric tube	LT4, 100 mcg, orally	LT4, 100 mcg, orally
TSH, mIU/L	0.74 (0.4-4.5)		1.52 (0.3-4.7)	<0.02 (0.55-4.78)	3.5 (0.3-4.7)	0.21 (0.3-4.7)
Free T4, ng/dL	0.6 (0.8-1.8)		0.4 (0.8-1.6)	0.7 (0.89-1.76)	0.6 (0.8-1.6)	0.7 (0.8-1.6)
Total T4, mcg/dL		4.0 (4.5-12.0)		2.7 (4.5-10.9)		
Free T4 index, mcg/dL		1.1 (1.4-3.8)				
Free T3, pg/ml	3.7 (2.3-4.2)					4.8 (2.2-3.8)
Total T3, ng/dL			52 (85-185)			
Reverse T3, ng/dL			12 (8-25)			7.3 (9-27)

## DISCUSSION

This case is unique in that it shows, for the first time, that high T3 syndrome can occur in a patient with massive metastatic PTC or PDTC. Although high T3 syndrome has been found in about 20% patients with massive metastatic FTC, it has not been reported in patients with massive metastatic PTC, medullary thyroid cancer (MTC), or PDTC (3). FTC expresses high levels and activities of deiodinase 1 (D1) and 2 (D2), both converting T4 to T3, which explains the

high T3 syndrome in patients with large burden of FTC (3, 4). It is not clear if the PTC, the PDTC, or both cause the high T3 syndrome in this patient. Classical and follicular variant of PTC can occasionally cause thyrotoxicosis so that they must be able to express D2 (the main enzyme that converts T4 into T3 in humans) at times; the free T4 and T3 levels are congruent in those cases, suggesting the D2 activity in PTC is usually not excessive(4-6). PDTC expresses lower levels of D2 than normal thyroid tissue or FTC, but expression of D1 is not studied in PDTC (7). It is thus possible

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that either PTC or PDTC expresses D2 or D1 which can convert endogenous or exogenous T4 to T3 if the tumor burden is large enough.

This case also highlights the importance of recognizing high T3 syndrome. Had the high T3 syndrome been recognized when he had normal TSH during critical conditions, the inappropriate increase of LT4 dose could have been avoided. The eventual, albeit delayed, recognition of high T3 syndrome also obviates the needs of expensive imaging of the pituitary. Clinical judgment can often reach a definitive thyroid function diagnosis in the face of incongruent test result (8). Assessment of T3 levels relative to T4 levels, however, is pivotal for recognizing high T3 syndrome, as shown in this case.

In summary, this novel case demonstrates that high T3 syndrome can also occur in a patient with PTC or PDTC. Additionally, the case illustrates the clinical relevance of recognizing this syndrome and the thyroid function test result profile leading to its diagnosis.

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**Citation:** Dr. Run Yu. *High T3 Syndrome Associated with Metastatic Papillary and Poorly Differentiated Thyroid Cancer.* *Archives of Diabetes and Endocrine System.* 2018; 1(1): 10-12

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