Persistent low Thyroglobulin Levels with Positive Post therapy Scan in Metastatic Differentiated Thyroid Carcinoma

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ABSTRACT

Background: The level of thyroglobulin (Tg) and 131 I whole-body scan (WBS) are essential for diagnosis of recurrent and persistent differentiated thyroid carcinoma (DTC) after radioactive iodine therapy (RAIT). Low Tg level has high negative predictive value for persistent disease. Tg negative DTC is a rare and diagnostically challenging manifestation within the spectrum of thyroid malignancies that complicates both diagnosis and management.

Aim/Objective: This study aims to comprehensively analyze the clinical characteristics, diagnostic approaches, and therapeutic strategies associated with low Tg metastatic DTC and to enhance our understanding of this unusual occurrence.

Patients and Methods: A retrospective analysis was conducted on seven diagnosed cases of Tg negative metastatic DTC, who received RAIT from National Institute of Nuclear Medicine and Allied Sciences (NINMAS), and they were selected randomly between the years 2007 to 2023. Patients received RAIT in doses ranging from 150 m Ci to a maximum of 1000 m Ci, given in single to as many as seven therapies. Three patients underwent re-surgery for the removal of metastatic masses. Clinical records, blood profile e.g. stimulated TSH, Tg, Anti TgAb (both initial and latest), imaging studies e.g. ultrasonography (USG), diagnostic whole-body scan (DxWBS)/ large dose scan (LDS), post therapy scan (RxWBS), CT scan, MRI, PET-CT, and FNAC, excisional biopsy, histopathology data were systematically reviewed to reveal this specific thyroid carcinoma subtype.

Results: A total of seven patients, six males and one female, were referred to NINMAS for RAIT. Age distribution was 30 to 70 years (median: 49 years). The average Tg level was 0.83 ng/ml and anti TgAb was <10.0 IU/ml. Five patients had Papillary Thyroid Carcinoma (PTC) and two had Follicular variant ? (FTC). Four of them presented with metastasis at initial meeting, whereas rest three developed metastasis gradually afterwards. Lymph node (LN) metastasis was noted in four patients, among them two had only cervical LN metastasis, one had cervical and intra-abdominal (para-aortic) nodal metastases, and the last one had inguinal lymph nodes involvement. Three patients had bone metastasis (vertebrae, ribs etc.), one had lung metastasis, one had intra-abdominal mass and one showed chest wall involvement. Metastasis were detected through USG, CT or PET- CT, Bone scan, WBS and later confirmed by histopathology. DxWBS/LDS was done in only three cases, two negative and one positive. Two patients received radiotherapy (RT) for bony involvement. Three patients underwent re-surgery for the removal of metastatic masses.

Conclusion: In conclusion, the patient's symptoms, clinical characteristics, and diagnostic modalities beyond conventional serum markers are needed for accurately identifying and monitoring disease progression in such cases.

Keywords: Thyroglobulin, Differentiated thyroid carcinoma, Metastasis, post therapy scan.

Bangladesh J. Nucl. Med. Vol. 27 No. 2 July 2024
DOI: https://doi.org/10.3329/bjnm.v27i2.79195

INTRODUCTION

Thyroglobulin (Tg) is excreted simply by thyroid cells and is one of the crucial factors in the follow-up of cases with differentiated thyroid carcinoma (DTC). Serum Tg level is a sensitive tumor marker for DTC. According to a meta-analysis, the extremely sensitive Tg assay's negative predictive value was 97% and 99% at basal Tg levels of >1 ng/mL and >2 ng/mL, respectively, as cutoffs for positive. (1). The highest amount of Tg is observed in bone metastases however, low Tg levels may be linked to lymph node metastases. Tg has a very high sensitivity for detecting bone metastases, particularly following activation with thyroid-stimulating hormone (TSH). Low Tg linked to normal neck ultrasonography is used in many clinical studies as evidence of therapy response and is said to have a very strong negative predictive value for persistent disease. In order to help with initial risk stratification and adjuvant therapy decision-making, prior research has shown the clinical utility of measuring thyroglobulin (Tg) (either TSH stimulated or non stimulated) before radioactive iodine (RAI) remnant ablation and after total thyroidectomy (postoperative Tg) (2). The sensitivity of monitoring both the Tg level and the 131-Iodine distribution on whole-body scan (WBS) is essential for the early diagnosis of recurring differentiated thyroid cancer (DTC) cells in post-surgery DTC patients (3).

Still false negative Tg is reported in 6.8% of patients with metastasis (4). Low Tg may be seen with poorly differentiated carcinoma or nonimmune reactive Tg (4). The presence of heterophile antibodies in the patient's serum has also been linked to falsely low or high Tg levels. Tg was assessed using two distinct methods in this investigation, and the results showed consistently low levels of both Tg and anti-Tg over the course of the follow-up years (5). Tg-negative DTC is a rare and diagnostically challenging manifestation within the spectrum of thyroid malignancies that complicates both diagnosis and management.

PATIENTS AND METHODS

A retrospective analysis was conducted on seven diagnosed cases of Tg negative metastatic DTC, who received radioactive iodine therapy (RAIT) from National Institute of Nuclear Medicine and Allied Sciences (NINMAS) who were selected randomly between the years 2007 to 2023. Patients received RAIT in doses ranging from 150 mCi to a maximum of 1000 mCi, given in single to as many as seven therapies. Three patients underwent re-surgery for removal of metastatic masses. Tg negativity was defined as a serum Tg level of ≤2 ng/mL and an TgAb level of 2 ng/mL, regardless of TgAb level. Serum Tg level measurements were repeated in the using three other commercial kits in three different laboratories. Clinical records, blood profile e.g. stimulated TSH, Tg, Anti TgAb (both initial and latest), imaging studies e.g. ultrasonography, DxWBS, RxWBS, CT scan, MRI, PET CT, and FNAC, excisional biopsy, histopathology data were systematically reviewed to reveal this specific thyroid carcinoma subtype.

RESULTS

A total of seven registered DTC patients of NINMAS who were in regular follow up after RAIT with persistently low Tg level with metastases were included in this study. Among them six were males and one was female. Age distribution was 30 to 70 years (median: 49 years). Stimulated average TSH was 49.97 IU/ml, initial average Tg level was 2.6

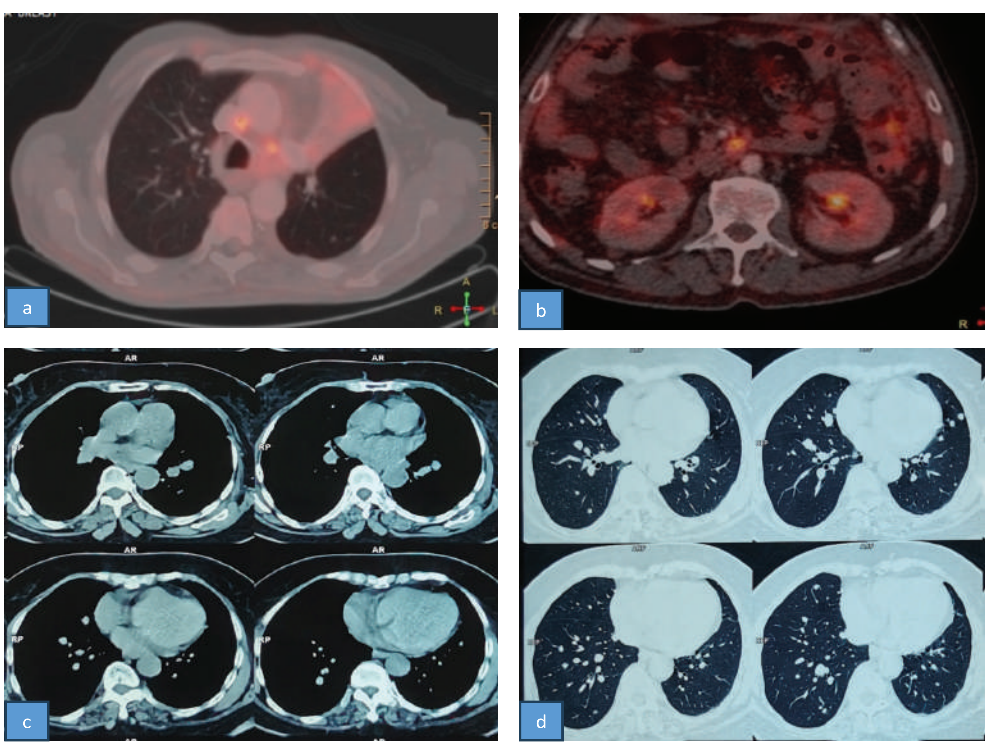

Figure-1: 18F FDG PET-CT scan showing intense FDG avid mediastinal (a) and abdominal lymph nodes (b) in a patient of PTC with persistently low Tg level. Chest HRCT showed mediastinal (c) and lung (d) window in a patient of PTC with low Tg level showing multiple nodular metastatic lesions in all lobe of both lungs.

ng/ml, TgAb level <10.0 IU/ml. In last follow up average Tg level was 0.71 ng/ml and anti TgAb was <10.0 IU/ml. Five had Papillary Thyroid Carcinoma (PTC) and two had Follicular variant (FTC). Four of them presented with metastasis at initial diagnosis, whereas rest three developed metastasis gradually afterwards. Lymph node (LN) metastasis was noted in four patients, among them two had only cervical LN metastasis, one had cervical and intra-abdominal (para-aortic) nodal metastases, and last one had inguinal lymph nodes involvement. Three patients had bone metastasis (vertebrae, ribs, skull etc.), one had lung metastasis, and one had intra-abdominal mass and one showed chest wall involvement. Metastases were detected by USG, CT, Bone scan, WBS, PET CT and later confirmed by histopathology. In RxWBS showed focal RTC in thyroid bed in all patients; bony uptake was noted in three patients, diffuse lung uptake in one case, left chest wall uptake was seen in one patient. DxWBS (LDS) was done in only three cases, two negative and one positive. Two patients had received radiotherapy (RT) for bony involvement. Three patients underwent re-surgery for the removal of metastatic masses.

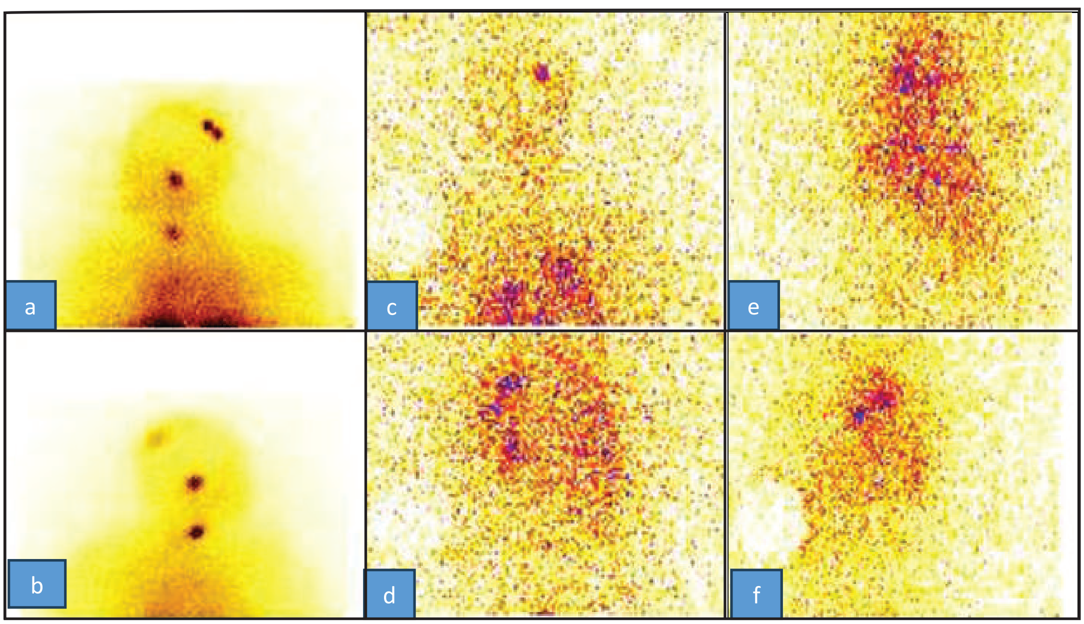

Figure-2: Post therapy scan showing intense RTC in left parietal bone (a,b); diffuse RTC in both lungs (c,d) and RTC in abdomen suggesting abdominal mass (e,f) in three different patients of PTC with persistently low Tg level.

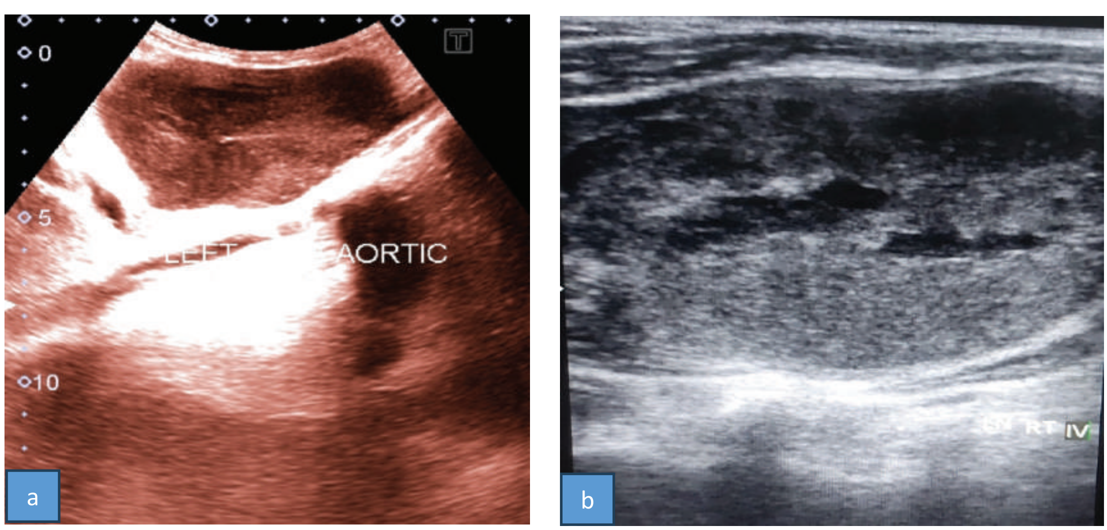

Figure-3: Ultrasound examination of a patient of PTC with persistently low Tg level showing multiple enlarged abdominal lymph nodes at left paraaortic (a) and right sided cervical (b) regions with loss of nodal architecture suggesting nodal metastases.

Table-1: Clinical details in metastatic DTC patients with persistently low thyroglobulin

Patient	Age/sex	Post operative Stimulated TSH- IU/ml	Stimulated Tg ng/ml	Initial TgAb IU/ml	Site of metastases at Diagnosis	RxWBS findings	Last Folow up Tg- ng/ml
1	70/male	72.87	1.9	26.5	Absent (cervical lymph node metastasis which developed later)	Focal RTC in thyroid bed	<0.20
2	49/male	22.09	1.2	1.30	Cervical and paraaortic lymph node, abdominal mass and C2 vertebra	Focal RTC in thyroid bed, let temporal bone,	0.59
3	48/male	92.59	2.7	3.9	C2,C3, 7th rib and left chest wall mass	RTC in thyroid bed and left side of chest wall	0.22
4	30/male	25.8	4.1	20	Absent (right cervical lymph node metastasis which developed later)	RTC in thyroid bed	0.92
5	55/male	30.8	6.8	6.3	Absent (Inguinal lymph node metastasis which developed later)	RTC in thyroid bed, Right lower chest and right side of abdomen	1.42
6	47/male	30.25	<0.20	1.3	Multiple bone and scalp	RTC in thyroid bed, Single foci in occipital bone; multiple dorsal vertebrae	2.35
7	55/female	75.4	1.3	4.6	Bilateral lungs	RTC in thyroid bed, Bilateral lung uptake	0.22

DISCUSSION

Thyroglobulin is frequently measured in follow-up of patients with DTC. A low-stimulated Tg level (<1 ng/ml) associated with normal neck ultrasonography is considered as the most reliable criterio for complete remission in low-risk patients. Also stimulated Tg between 1 and 10 ng/ml concomitant with normal neck ultrasonography is considered an "acceptable response" (6). However, false-negative Tg in the presence of metastasis is reported in 6.8% of patients (4). . Another study in 194 patients with differentiated thyroid carcinoma (DTC), with a mean follow-up of 7.7 yeas, found persistent disease in 1.5% of the patients. In that study, there was no patient with a low serum Tg level concomitant with distant metastasis (7).

Low Tg may be seen with poorly differentiated carcinoma or nonimmunoreactive (5). 5). Falsely low or high Tg evels are also reported in the presence of heterophile antibodies in the serum of the patient. In our study, Tg was measured with two different techniques and showed persistently low Tg and anti-Tg levels throughout the years of follow-up.

Inappropriate low serum Tg level in the presence of widespread skeletal metastases was noted in spite of measurement of Tg with two different kits and controlling for heterophile antibodies. In this study, both CLIA and radiometric assay (RIA) methods were applied. For in vitro diagnostic use with the IMMULITE® 2000 Systems Analyzers — for the quantitative measurement of thyroglobulin in serum or heparinized plasma, as an aid in monitoring patients who have undergone thyroidectomy. Only a few cases of skeletal metastases associated with low Tg levels were reported in the literature, and only one of the reported cases had diffuse skeletal metastases (8). In this reported case, skeletal metastases were found in three cases among the seven cases with low Tg levels.

For the majority of these individuals, early detection and radioiodine therapy are essential in order to reduce long-term morbidity and maybe increase survival. The patient's lack of symptoms despite extensive bone metastases is the other lesson learnt. This conclusion highlights the importance of closely examining DTC individuals and not relying just on their symptoms and Tg level. The noteworthy aspect in these seven cases was that there was a rapid progression in the context of low serum Tg level, despite multimodality treatment instituted and early diagnosis. All the cases showed very low stimulated Tg and minimal ^{131}I uptake in the lesions. This demonstrated that determining the disease burden required more than just using standard methods for disease detection, such as local USG, stimulated Tg, and ^{131}I scan. According to research by Ibrahimpasic et al., in 2015 the prognosis was better for those who were poorly DTC, had no macroscopic disease, and had undetectable serum Tg levels (9). The two cases in this study had rapid disease progression of the macroscopic disease, consistent with the inherently aggressive nature of DTCs. An evidence-based review by Sanders et al. in 2007 suggested this subgroup may benefit from aggressive treatment, although the role of radioiodine was not conclusive (10). External beam radiotherapy (EBRT) is recommended by extrapolating data from well DTC with high-risk features. However, some studies have shown I-131-avid disease, and that postsurgical radioactive iodine therapy is useful and early diagnosis is essential for PDTC (11,12). Furthermore, the role of multikinase inhibitors and the appropriate time for their initiation are not clearly defined. From the genomic perspective, BRAF, MAPK, and histone deacetylase (HDA1C) inhibitors may be beneficial for a selective group of patients (13,14). But they need further clinical data for their routine use. Therefore, there is a need for such studies to formulate appropriate management of DTC so as to maximize patient benefit.

DTCs with minimal/low ^{131}I avidity and low serum Tg levels but with macroscopic disease clinical signs and symptoms of disease progression need close monitoring and other diagnostic modalities, including FDG/68Ga- DOTATATE PET-CT and USG, with the development of an appropriate diagnostic and treatment algorithm.

CONCLUSIONS

Low Tg levels and absence of symptoms do not exclude widespread metastases in patients with DTC. Behavioral heterogeneity can be observed within the same histopathological subtype of DTC with respect to their Tg secretor and radioiodine avidity. Their clinical course and management need to be individualized.

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