The Thyroglobulin Paradox; An Enigmatic Case Report of Thyroid Carcinoma with Skeletal Metastasis

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ABSTRACT

Thyroglobulin (Tg) is frequently measured in follow-up of patients with differentiated thyroid carcinoma after total thyroidectomy and radioiodine therapy. A low stimulated Tg level (<1 ng/ml) associated with normal neck ultrasonography is considered as the most reliable criteria for complete remission in low-risk patients. We are reporting a case of middle-aged man with thyroid cancer and diffuse skeletal metastasis associated with low serum Tg level bringing a point of caution in evaluation of patients with low Thyroglobulin.

Keywords: Bony metastasis, Papillary thyroid carcinoma (PTC), Thyroglobulin (Tg), Anti Thyroglobulin antibody (Anti Tg).

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INTRODUCTION

Thyroid carcinoma is an emerging health issue in Bangladesh and also worldwide. It is considered the most common endocrine malignancy in the country, often found in about 18-33% of patients with symptomatic thyroid nodule and usually occurs in third to fourth decades of age. Thyroglobulin is a glycoprotein produced exclusively by thyroid follicular cells. Following total thyroidectomy and radioiodine ablation, it serves as a highly sensitive tumor marker for detecting recurrence and metastasis, while highest level of thyroglobulin (Tg) are typically observed in patients with bony metastasis. However, a small subset of patients presents with Tg negative or low Tg in metastatic disease.

Bone is the second most common site of distant metastasis in thyroid malignancy after the lung; occurs approximately 1-7% cases. Bony metastases are associated with poor prognosis and adverse skeletal events like fracture and compression etc. This report notifies a rare case of a middle-aged man who presented with papillary carcinoma of thyroid and skeletal metastasis despite having low Tg.

CASE REPORT

A 48-year-old man initially presented with soft tissue swelling over the left lower chest, while the primary lesion was identified as papillary carcinoma of the thyroid. The patient was referred to the thyroid division of NINMAS after a total thyroidectomy and 30 Gy of preoperative radiotherapy in 10 fractions for skeletal involvement. Bony metastasis was evident on preoperative bone scintigraphy and subsequent PET-CT, which showed hypermetabolic lytic lesions with adjacent soft tissue components in the 7th rib and lamina and pedicles of C2 and C3 vertebrae. Laboratory reports showed TSH = 92.59 uIU/ml and an exceptionally low Tg level of 2.72 ng/ml; anti-Tg antibody = 3.92 IU/ml. Surgical excision of the left chest wall mass was advised, but the patient was not willing to comply. Eventually, an ablation dose of 200 mCi radioiodine (131I) was administered, and a post-therapy whole-body scan (RxWBS) revealed intense radioiodine uptake in the thyroid bed and left chest wall, corresponding to the chest CT finding. However, the serum Tg level was persistently low (0.22 ng/ml).

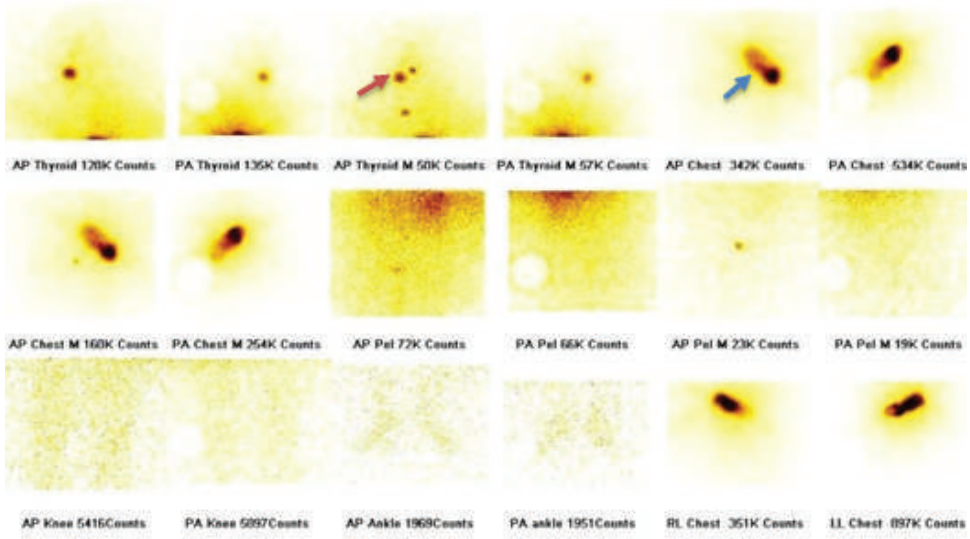

Figure 3: Post therapy ^{131}I whole body scan showing focal area of radiotracer concentration in thyroid bed (red arrow) with large focal area of intense radioiodine concentration in the left side of chest wall (blue arrow).

Six months later, a second radioiodine therapy dose of 200 mCi was administered and RxWBS showed intense RTC over the thyroid bed, left chest wall, and cervical region, with increased intensity compared to the previous scan. Patient underwent surgical excision of the soft tissue mass in the 6th-8th rib area, histopathologically reported as follicular variant of papillary thyroid carcinoma. Subsequent CT scan identified small nodules in both lung fields and mild pleural effusion.

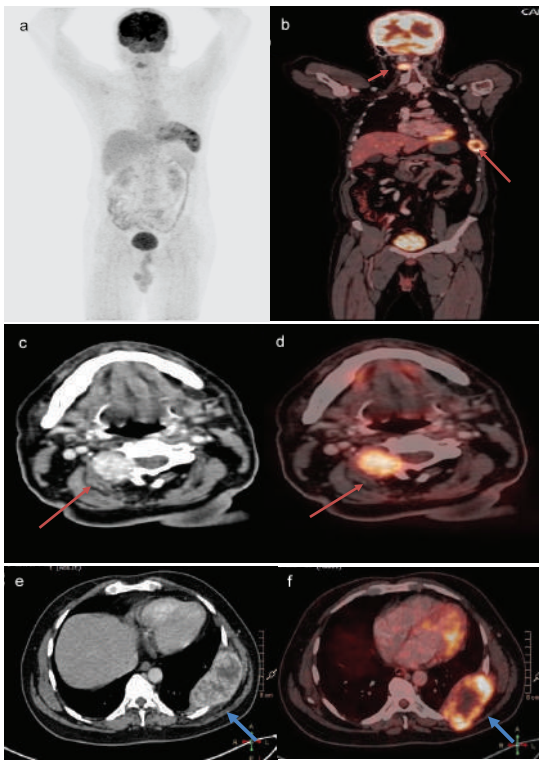

Figure 4: 18 F FDG PET-CT MIP (a), coronal image (b), along with axial (c,d,e,f) PET-CT images showing FDG avid (SUV max: 19.94) lytic lesion with adjacent soft tissue component in lamina, pedicle and transverse process of C2 vertebra (3.2 X 2.8 X 2.3 cm) on right side (c,d) (red arrow). Another FDG avid (SUV max: 6.61) expansile lytic lesion with adjacent large soft tissue component (11.55 X 6.29 X 5.90 cm) in 7th rib on left side (e,f) (blue arrow) was confirmed as metastatic adenocarcinoma through histopathology.

Recently the patient underwent a third radioiodine ablation of 200 mCi, resulting in no recurrent thyroid cancer detected on the post-therapy scan, except for minor findings in the mid-chest wall. Laboratory results indicated a Tg level of 5.84 ng/ml and an anti-Tg level of 60.24 IU/ml. The patient reported relatively good health during the visit, with only mild chest pain and leg cramping noted.

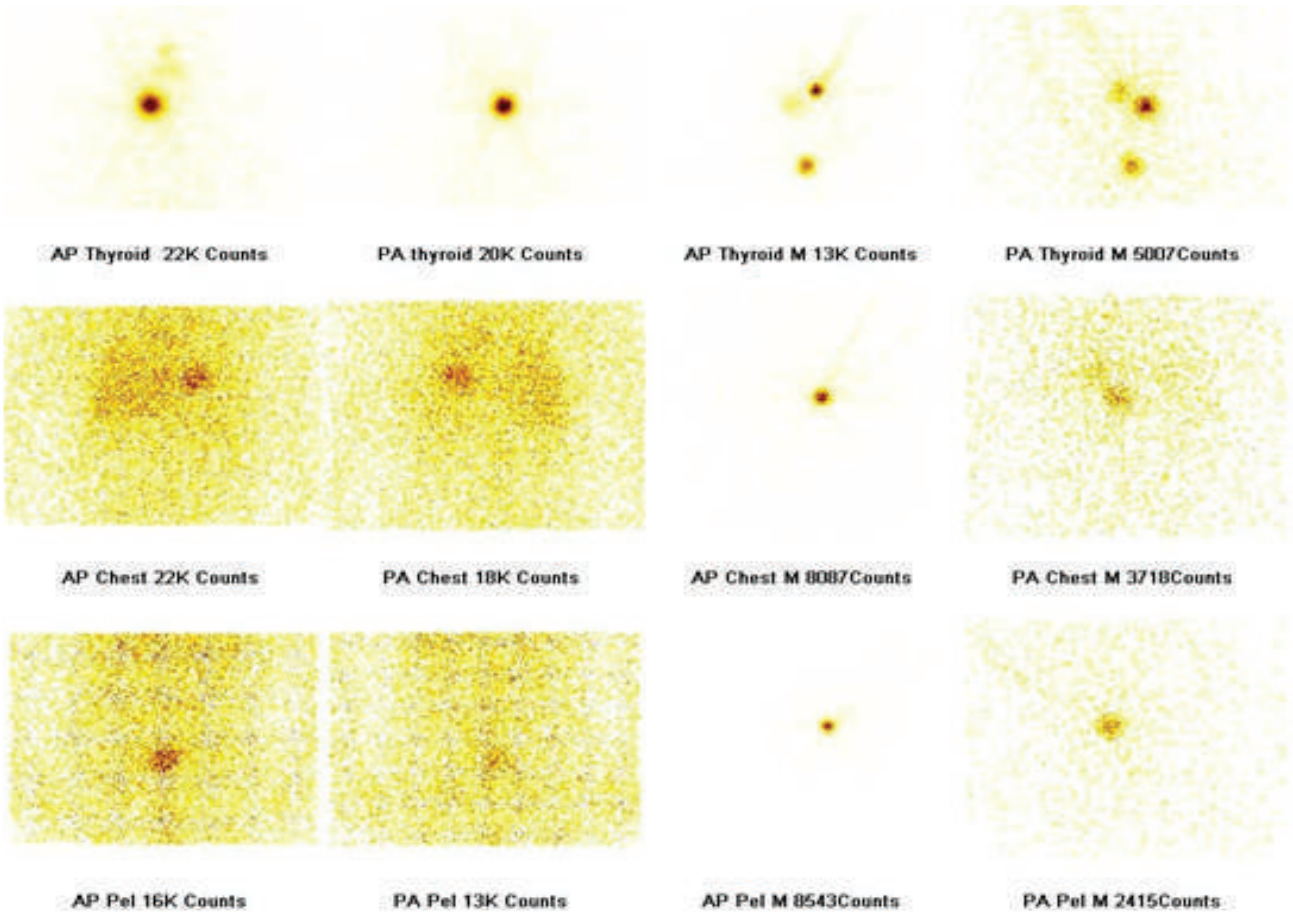

Figure 5: Post therapy 131I whole body scan showing no radioiodine concentration in thyroid bed.

DISCUSSION

Thyroglobulin (Tg) is usually measured to evaluate the follow-up of patients with differentiated thyroid carcinoma (DTC) after total thyroidectomy and radioiodine therapy. In multivariate analysis, the postoperative Tg is often found to be an independent predictor of persistent/recurrent diseases (1). High levels of postoperative Tg values (>10–30 ng/mL) are associated with poorer survival (2, 3). Conversely, postoperative stimulated Tg values less than 1 to 2 ng/mL are strong predictors of remission (4). If total thyroidectomy and RAI ablation are performed, an excellent response is usually defined as a TSH-stimulated Tg level of less than 1 ng/mL in the absence of structural or functional evidence of disease (and in the absence of Tg antibodies) (5). Here, we report a case of papillary carcinoma of thyroid with skeletal metastases associated with a very low serum Tg level.

Tg can be low in patients with metastases; Park et al. reported a retrospective analysis of 824 consecutive patients with DTC (6). According to their results, only 7 of them (0.8%) had distant metastases to lung or bone with a low serum Tg level. This so-called false-negative Tg determination phenomenon can be explained by the following several reasons (6, 7). First, technical issues might cause a false Tg-negative result. In particular, antigen levels 10 to 10,000 times the upper limit of the assay range can exceed the binding capacity of antibody

for the solid support (9). Second, according to Brendel et al., reduced Tg synthesis and/or the release or synthesis of a Tg variant that routine radioimmunoassays cannot recognize could lead to lower Tg levels, which often occurs in marginally differentiated metastatic tumors. Alternatively, Tg might be cleared more rapidly from plasma (10). Third, the Tg structure has changed. Part of malignant transformation can change Tg's structure (genetic variant) by reducing the iodine content and the amounts of several amino acids and monosaccharides. (10) Park et al.'s Tg determination phenomenon can be explained by the following several reasons: First, technical issues might cause a false Tg-negative result. Second, reduced Tg synthesis and/or the release or synthesis of a Tg variant that routine radio immunoassays cannot recognize could lead to lower Tg levels, which often occurs in marginally differentiated metastatic tumors. (7-9).

Thirdly, the thyroglobulin (Tg) structure has been changed as a part of malignant transformation (genetic variant) by reducing the iodine content and the amounts of several amino acids and monosaccharides. Low Tg may also be seen with poorly differentiated carcinoma or non-immune reactivity (2). Falsely low or high Tg levels are also reported in the presence of heterophile antibodies in the serum of the patient (5). 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. An inappropriately 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, the patient had skeletal metastasis despite being responsive to radioiodine therapy. For the majority of these individuals, early detection and radioiodine therapy are essential in order to reduce long-term morbidity and maybe increase survival. This conclusion highlights the importance of closely examining DTC individuals and not relying just on their symptoms and Tg level. The noteworthy aspect in this case was that there was a rapid progression in the context of a low serum Tg level, despite multimodality treatment instituted and early diagnosis. This demonstrated that determining the disease burden required more than just using standard methods for disease detection, such as local USG, stimulated Tg, and iodine 131 scan (10). In our case, the patient was amenable to surgical therapy, radiotherapy, and a total of 600 mCi of radioiodine therapy. In such cases, we suggest that alternative treatment, such as tyrosine kinase inhibitors, may be worthy of consideration to prevent the related events.

External beam radiotherapy (EBRT) is advised based on data from well-differentiated thyroid carcinoma (DTC) with high-risk genomic features. BRAF, MAPK, and histone deacetylase (HDA1C) inhibitors may benefit a select patient group, though more clinical data is needed for their routine application.

CONCLUSION

Reported case of differentiated thyroid carcinoma highlighted that low Tg levels and lack of symptoms can occur despite widespread metastases. The patient's management proved challenging but he responded well to radio-iodine therapy, maintaining relatively good health. Unusually, his Tg levels remained persistently low, which may relate to genetic and behavioral heterogeneity within the same histopathological subtype. This necessitates individualized clinical management and assessment considering variations in radioiodine and FDG avidity.

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