

Diffuse skeletal metastasis and low thyroglobulin level in a pediatric patient with papillary thyroid carcinoma

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ABSTRACT

Thyroglobulin (Tg) is frequently measured in follow-up of patients with differentiated thyroid carcinoma. 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 pediatric thyroid cancer with diffuse skeletal metastasis associated with low serum Tg level bringing a point of caution in evaluation of patients with low Tg.

Keywords: Bone metastasis, papillary, thyroglobulin, thyroid cancer, whole body iodine scans

INTRODUCTION

Thyroglobulin (Tg) is excreted exclusively by thyroid cells and is one of the key factors in the follow-up of patients with follicular differentiated thyroid carcinoma (FDTC). While lymph node metastasis may be associated with low Tg levels, the highest level of Tg is seen in bone metastasis. The sensitivity of Tg is very high for detection of bone metastasis especially after thyroid stimulating hormone (TSH) stimulation. Low Tg associated with normal neck ultrasonography is reported to have a very high negative predictive value for persistent disease and is used in many clinical trials as a proof of patient response to treatment. We are reporting a patient with diffuse skeletal metastasis associated with low serum Tg level bringing a point of caution in evaluation of patients with low Tg.

CASE REPORT

A 23-year-old man presented to our thyroid cancer clinic on May 2006 with a history of papillary thyroid carcinoma (PTC).

He was operated about 10 years ago with no follow-up and no radio-iodine therapy. Primary pathology was PTC in a 4.5 cm × 4.0 cm × 3.0 cm nodule in the right thyroid lobe. The stage of the disease at the time of diagnosis was considered pT3NxMx. On presentation, he had no symptoms and neck examination revealed a small 1 cm mass in the thyroid bed in midline. He underwent repeat neck exploration, and pathology examination revealed adenomatous nodule.

Following discontinuation of Levothyroxine for 4 weeks, thyroid values were measured in the serum and TSH was 150 mIU/L, Tg level was 3.5 ng/ml and anti-Tg antibody level was 11 IU/ml. The BIOCODE (S.A, Liege, Belgium) kit was used for determination of Tg level with a sensitivity of 0.35 ng/ml and an inter assay variation of 4.8% and between assay variation of 6.1%. After 2007, Tg measurements were done using Elecsys_electrochemiluminescent immunoassay from Roche Diagnostics (Meylan, France). Anti-Tg antibody was measured using ELISA method (Trinity-Biotech) before 2007 and by Elecsys electrochemiluminescent immunoassay from Roche Diagnostics (Meylan, France) after 2007. Diagnostic whole body iodine scan was performed 2 days after administration of 74 MBq I-131 and widespread bone metastasis, regional lymph node metastasis, and thyroid bed uptake was detected [Figure 1]. Patient had no complaint and after asking him about any bone pain, remembered just occasional mild low back pain.

The patient was treated with 7400 MBq of 131-iodine. Postablation whole body iodine scan (WBIS) was identical to diagnostic WBIS.

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Suppressive therapy was started, and measurement of Tg was done after discontinuation of the drugs 8 months later. TSH level was 380 mIU/ml with simultaneous Tg level of 6 ng/ml and anti-Tg antibody level of 11 IU/ml. Treatment was repeated with another dose of 7400 MBq of I-131. Postablation whole body iodine scan again showed multiple foci of metastases with no significant change compared with the previous scan. Radiography of the pelvis showed a small lytic lesion in the iliac bone with a rim of sclerosis [Figure 2a].

Since that time, the patient has been treated 5 more times with ^{131}I (total accumulated dose 51.8 GBq I-131). Tg level was always below 6 ng/ml in spite of multiple bone metastases. Thoraco-lumbar computed tomography scan was done for more confirmation and indicated the presence of skeletal involvement corresponding to the lytic lesions detected in the radiographies [Figure 2b]. The patient underwent surgical biopsy from the lumbar spine (L2) and the pathology result was positive for metastatic carcinoma. Immunohistochemistry of the removed tissue was positive for thyroid transcription factor-1 and Tg markers in tumoral cells, confirming thyroid origin of the lesions [Figure 3].

DISCUSSION

Thyroglobulin is frequently measured in follow-up of patients with FDTC. 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. Also stimulated Tg between 1 and 10 ng/ml concomitant with normal neck ultrasonography is considered as “acceptable response.”^[1] However false negative Tg in the presence of metastasis is reported in 6.8% of patients, although most of the patients in this report had only lymph node metastasis and only one patient had bone metastasis.^[2] Another study in 194 patients with differentiated thyroid carcinoma (DTC), with a mean follow-up of 7.7 years found persistent disease in 1.5% of the patients. In that study, there was no patient with low serum Tg level concomitant with distant metastasis.^[3]

Low Tg may be seen with poorly differentiated carcinoma or nonimmunoreactive Tg.^[4] Falsely low or high Tg level is also reported in the presence of heterophile antibodies in serum of the patient. In our study Tg was measured with two different techniques and showed persistently low Tg and anti-Tg level throughout the years of follow-up.

In the present patient, 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. Only few cases of skeletal metastases associated with low Tg level was reported in the literature, and only one of the reported cases had diffuse skeletal metastases.^[5] Our patient brings more caution in definition of response as low Tg and normal neck ultrasonography.

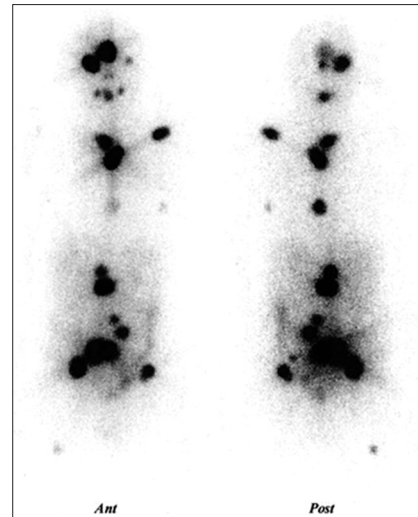


Figure 1: Postablation whole body iodine scan (anterior and posterior views) performed 7 days after 7400 MBq of I-131 shows multiple areas of iodine uptake in the skull, sternum, thyroid bed, cervical spine, left clavicle, thoracic spine, lumbar spine, pelvis and left femoral diaphysis

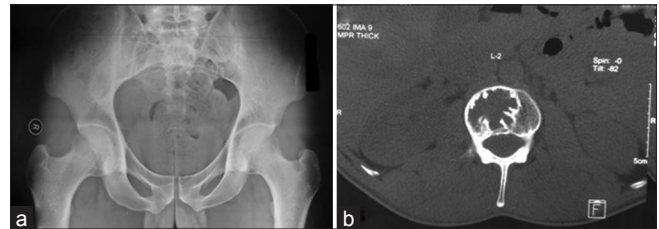


Figure 2: (a) Pelvic radiography shows lytic lesion in the right iliac bone with a rim of sclerosis. (b) Computed tomography scan image from 2nd lumbar spine shows a lytic lesion in the vertebral body with sclerotic rim and internal septa. Mild expansion also is noted. These findings strongly suggest low grade malignant lesion

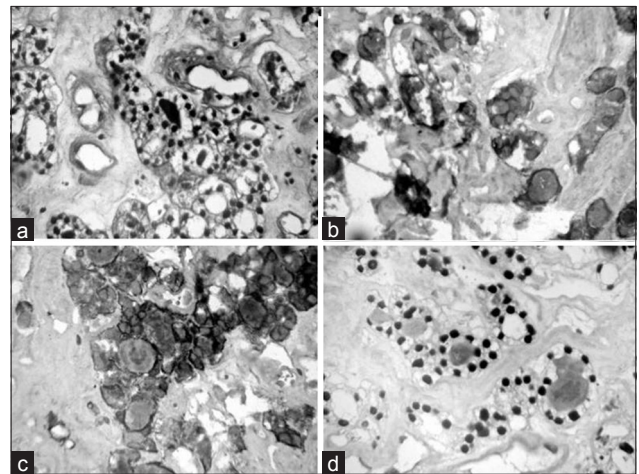


Figure 3: (a) Carcinoma cells with follicle-like structure formation (H and E, $\times 10$). (b and c) immunohistochemistry study show positive cytoplasmic immunoreactivity for thyroglobulin. (d) Positive nuclear immunoreactivity for thyroid transcription factor-1

Our patient is a case of pediatric thyroid cancer, operated at the age of 13 years old. As distant metastases are more commonly seen in pediatric patients, diagnostic WBIS may be useful in these patients irrespective of the result of Tg or neck ultrasonography.

Early recognition and radio-iodine therapy are mandatory in the majority of these patients to prevent long term morbidity and possibly to improve survival.

The other teaching point in our patient is absence of symptoms in spite of widespread skeletal metastasis. This finding again emphasizes on careful scrutiny in patients with DTC and not relying only on Tg level and symptoms.

CONCLUSION

Low Tg level and absence of symptom does not exclude widespread skeletal metastases in patients with PTC.

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