Case-Based Literature Review

Incidental detection of hyperfunctioning thyroid cancer metastases in patients presenting with thyrotoxicosis

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ABSTRACT

Thyrotoxicosis due to functioning metastases from thyroid cancer is rare. It also presents a therapeutic challenge, as both the metastatic cancer and thyrotoxicosis need to be treated. We present here two cases of thyrotoxicosis which on a routine ^{99m}Tc-pertechnetate thyroid scan showed extrathyroidal foci of uptake. Two patients who initially presented with thyrotoxicosis underwent a routine thyroid scan. Abnormal uptake in the shoulder was incidentally noted, which prompted us to do a whole body pertechnetate scan in the same sitting, which revealed extensive hyperfunctioning metastases in the lungs and bones. We also discuss the 'Flip Flop' phenomenon in thyroid cancer, which was seen in our case. This report emphasizes the importance of evaluating the abnormal foci of uptake seen on a routine thyroid scan.

Key words: Hyperfunctioning metastases, thyroid cancer, thyrotoxicosis

Introduction

Thyrotoxicosis due to functioning metastases from thyroid cancer is a rare occurrence. It also presents a therapeutic challenge, as both the neoplastic disease as well as thyrotoxicosis has to be dealt with. Few cases have been reported in literature of functioning thyroid metastases causing toxicity. Radioactive iodine uptake and ^{99m}Tc pertechnetate thyroid scan are investigations routinely employed in the clinical workup of thyrotoxic patients. We present here two cases of thyrotoxicosis, which on a routine ^{99m}Tc-pertechnetate thyroid scan showed extrathyroidal foci of uptake subsequently leading to the diagnosis of metastastic thyroid cancer.

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Case Reports

Case 1

A 65-year old male patient presented to the endocrinologist for evaluation of thyrotoxicosis. He was thyrotoxic since six months and on antithyroid drug carbimazole 5 mg TDS, which failed to achieve euthyroidism. Four months ago, the patient developed a right sided thyroid nodule. Fine needle aspiration cytology (FNAC) of the same revealed a follicular neoplasm. The patient underwent a subtotal thyroidectomy at another institution. Histopathology revealed follicular carcinoma of the right lobe, with adenomatous goiter of the left lobe. After a transient phase of two months in which the toxic symptoms reduced post surgery, the patient had a toxic recurrence and he was referred to our institution for a pertechnetate thyroid scan. The pertechnetate thyroid scan showed minimal tracer uptake in the thyroid bed. Incidentally, intense tracer concentration was noted in the left shoulder. A pertechnetate whole body scan was done in the same sitting to explore any other abnormal sites of uptake, which revealed foci in both lungs and bilateral pelvic bones [Figure 1].

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^{131}I whole body scan with 1.2 mCi also confirmed the above-mentioned sites of uptake [Figure 2]. Twenty-four hours of RAIU was 0.6% in the neck and 7% over the left shoulder. Serum thyroglobulin was in the metastatic range (>300 ng / ml) with negative anti-Thyroglobulin antibodies.

^{18}F-FDG PET / CT showed no pulmonary lesions, but confirmed the bony lesions mentioned earlier in the text [Figure 3].

On the basis of these findings the patient was admitted for high-dose radioiodine therapy. Pre-radioiodine clinical examination revealed a high pulse rate of 112 / minute, tremors, and increased perspiration. T3 was 430 ng / dl, T4 15.3 ug / dl, and TSH 0.03 mIU / L. Pretreatment with high doses of antithyroid drugs — carbimazole 20 mg TDS and beta blocker — and also propanolol 40 mg TDS was given and continued during the ^{131}I therapy, to avoid complications due to release of excessive thyroid hormones by the hyperfunctioning metastatic lesions. 200 mCi (7.4 GBq) of ^{131}I was given in view of the bone metastases. Radiation monitoring at 1 m distance was done daily. The patient was discharged on day seven when the radiation level dropped to less than 30 microsieverts per hour. A post therapy ^{131}I whole body scan was done on discharge, which showed iodine concentration in the known lesions. No new lesions were detected. The patient followed up for the next dose of radioiodine after six months. At this time he had become hypothyroid and was put on 150 μg thyroxine daily. The patient has further undergone six cycles of radioiodine therapy (200 mCi each) and has had no recurrence of thyrotoxicosis over the last five years. His stimulated serum thyroglobulin, however, remains in the metastatic range (> 300 ng / ml).

Case 2

A 62-year-old male, a farmer by profession, presented to the physician with chief complaints of breathlessness, bilateral chest pain, and fever since three months. He had a history

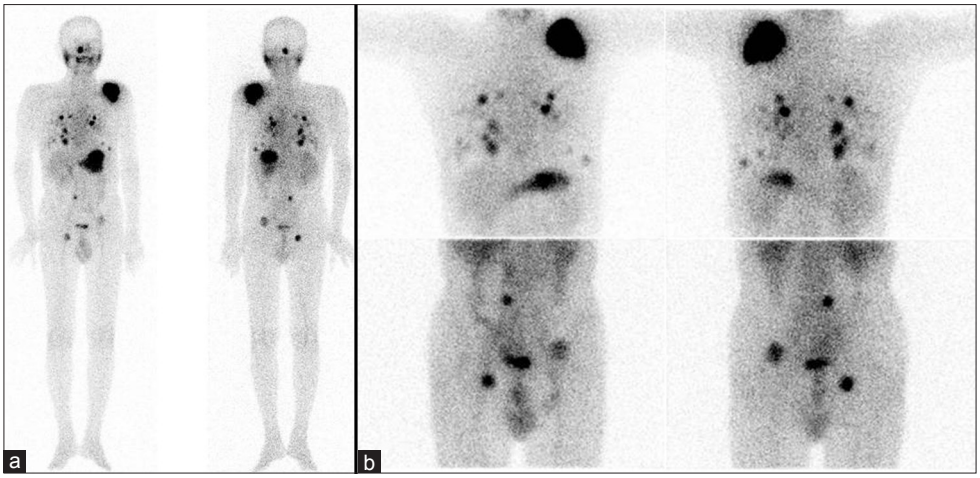

Figure 1: (a, b) ^{99m}Tc-pertechnetate whole body scan showing intense radiotracer uptake in the left shoulder, bilateral lungs and pelvis

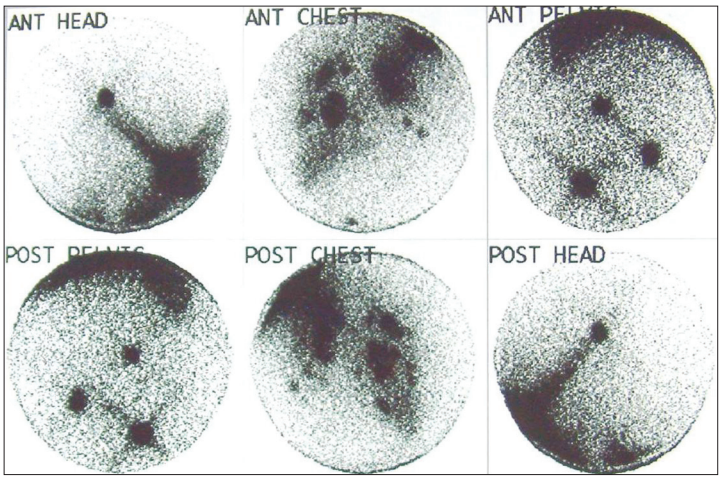

Figure 2: ^{131}I- whole body scan showing intense radiotracer uptake in the left shoulder, bilateral lungs, and pelvis

of pulmonary tuberculosis two years ago, for which he was treated with antituberculous drug therapy for six months.

On general examination he was found to have a pulse rate of 110 / minute and respiratory rate of 24 / minute, with normal blood pressure (BP).

Systemic examination revealed swelling of the left seventh to tenth ribs posteriorly. He was evaluated with a thyroid profile that was found to be in a toxic range, with undetectable TSH. Anti-TPO and anti-Tg antibodies were negative. The patient was referred to the Nuclear Medicine Department for radioactive iodine uptake (RAIU) and thyroid scan. Two- and Twenty-four-hour thyroidal uptake was 1 and 0%, and the thyroid scan also revealed no uptake in the region of the thyroid, but a focus of intense uptake was seen incidentally in the skull and left shoulder.

A whole body pertechnetate scan, in the same sitting, revealed multiple foci of intense tracer uptake in the bilateral ribs and sternum including a large focus extending from the left seventh to tenth ribs laterally. Multiple foci in the pelvis and sacrum were also found. A chest radiograph showed intrathoracic–extrapleural soft tissue mass involving the left seventh to tenth ribs [Figure 4].

Figure 3: ^{18}F-FDG PET showing increased tracer uptake in the left shoulder and pelvis

Subsequently, the patient underwent an ultrasound-guided biopsy from the left-sided chest wall lesion, which revealed follicular cells. This created a suspicion of metastatic thyroid cancer. Immunohistochemistry was done [Figure 5]. It revealed the cells to be positive for thyroglobulin, focally positive for CK19, and negative for TTF1. The patient underwent contrast-enhanced computed tomography (CECT) chest, skeletal survey and X-ray dorsolumbar spine, which revealed multiple metastases in the chest wall and D6, D7 vertebrae, and destruction of the L5, S1 vertebrae [Figure 4]. Subsequently, the patient underwent a neck ultrasound, which revealed multiple heteroechoic lesions in both lobes of the thyroid, including a large nodule in the left lobe lower part. Ultrasound-guided FNAC revealed a follicular neoplasm.

Serum Thyroglobulin was in the metastatic range (> 300 ng / ml) with negative anti-thyroglobulin antibodies.

The patient was started on Carbimazole 15 mg TDS and Propranolol 40 mg BD. The patient's thyroid profile improved on antithyroid drugs in three weeks, but worsened again over the next two weeks. As the patient was deemed to be a poor candidate for surgery, a decision to give radioiodine as a palliative therapy was taken. He was treated with high doses of the antithyroid drug carbimazole, 20 mg TDS, and the beta blocker Propanolol 40 mg TDS, starting one week prior, and continuing during, and three weeks after radioiodine therapy. The patient was treated

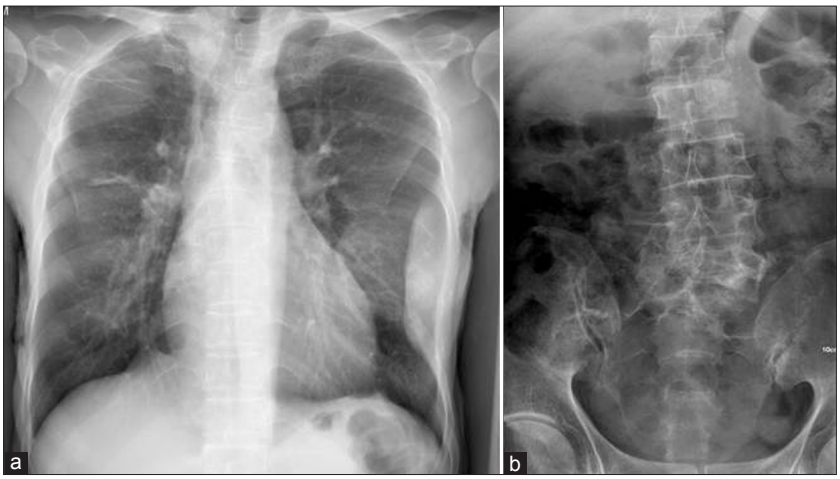

Figure 4: (a) Chest radiograph showing intrathoracic–extrapleural soft tissue mass involving the left seventh to tenth ribs. (b) Radiograph showing destruction in the L5 and S1 vertebrae

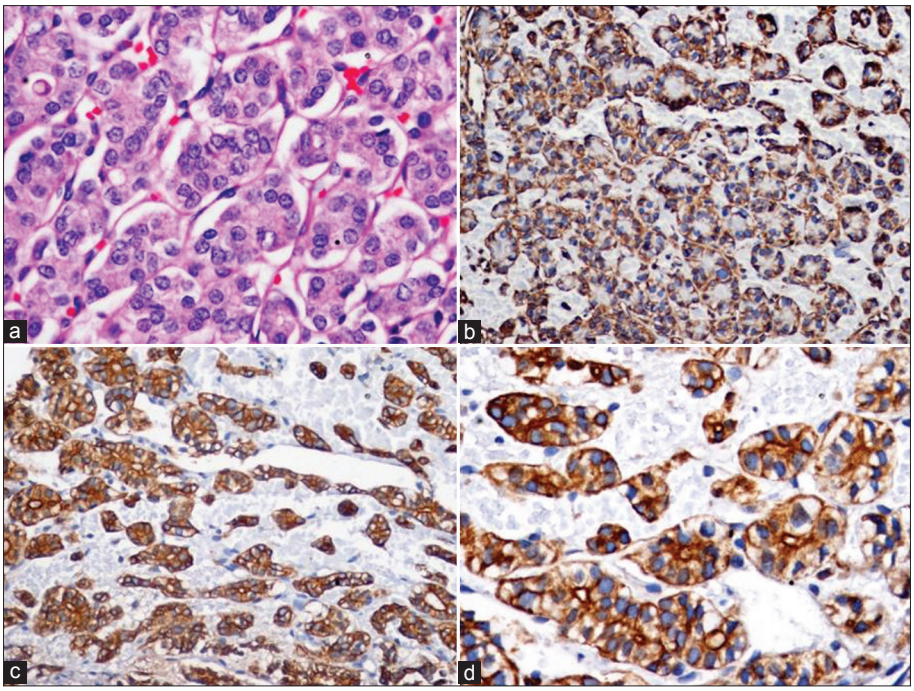

Figure 5: (a-d) H and E photomicrographs showed a tumor with repetitive arrangement of micro-follicles as seen in lower magnification (×40). Higher magnifications (×400) demonstrate the characteristic nuclear features of hyperchromasia, clearing, and occasional grooves, suggestive of a Follicular variant of papillary carcinoma. The neoplastic cells show membranous and cytoplasmic positivity for CK19, CK7, and thyroglobulin

with 100 mCi (3.7 GBq) radioiodine. Serial monitoring showed excellent whole body retention and the patient was discharged after seven days. A post therapy whole body scan corroborated the findings of the pre-therapy scan and no new lesions were detected. Four weeks after radioiodine therapy, his thyroid profile improved and he had improvement in his symptoms of thyrotoxicosis and chest pain. The patient continued on 15 mg TDS carbimazole and 20 mg TDS propranolol. He subsequently underwent radioiodine ablation four times more, over three years, thus totaling 700 mCi in five doses. He became clinically and biochemically euthyroid after the third dose, at which time his antithyroid drug and beta blocker were stopped. He became hypothyroid after the fifth dose of radioiodine. His serum thyroglobulin, however, has remained in the metastatic range (> 300 ng / ml).

Discussion

Thyrotoxicosis occurring in differential thyroid carcinoma (DTC) due to functioning metastases is rare. The various diagnostic possibilities of thyrotoxicosis associated with DTC have been detailed by Salvatori *et al.,* including Graves's disease, toxic multinodular goiter, and even struma ovarii.[1] In 1946, Leiter *et al.*[2] described the first patient with hyperthyroidism due to metastatic thyroid cancer. Once the diagnosis was made, therapy was directed toward treating both thyrotoxicosis and metastasis. Thyroid cancer is a well-differentiated endocrine malignancy and the metastatic cells are also well-differentiated like normal thyroid cells and retain the physiological properties of thyroid cells.[3] Age at diagnosis, gender, and cause-specific survival (CSS) is comparable with DTC, presenting with functioning or non-functioning metastases (CSS at 10 years: 59% in patients presenting with functioning metastases vs. 55% with non-functioning metastases).[1,4,5]

The following criteria should be met to reach a diagnosis of hyperthyroidism due to the overproduction of hormones by metastatic tissue:

a. Failure of hyperthyroidism to resolve after adequate thyroidectomy
b. Exclusion of hyperfunctioning diffuse or nodular thyroid gland
c. Demonstration of radioiodine uptake by metastatic lesions
d. Low or absent thyroid radioactive iodine uptake

A ^{99m}Technetium pertechnetate thyroid scan is routinely used to differentiate the causes of thyrotoxicosis, and incidentally, we found intense uptake in the left shoulder in patient 1 and in the skull in patient 2, which made us proceed with the whole body $^{99m}TcO_4^-$ scan. This shows the impact of the scintigraphic findings in determining the correct management of patients who are at risk of undergoing inappropriate treatment.

Thyroid stimulating immunoglobulins (TSIs), also known

as long-acting thyroid stimulators (LATS), may be the reason for the metastasis to become functional. These LATS stimulate the TSH receptors, promoting growth of thyroid cancer cells, and this ultimately causes the large bulky metastatic tumors to function autonomously and synthesize the excessive thyroid hormones.[1]

Intense uptake of ^{131}I in the metastases, in spite of the suppressed TSH levels noted in both our cases, indicate that the bulky lung and skeletal tumor masses led to hyperproduction of the hormone causing thyrotoxicosis. Hyperthyroidism, which persisted even after subtotal thyroidectomy in patient 1, with low iodine uptake in the thyroid bed and incidental uptake in the left shoulder in the $^{99m}TcO_4^-$ thyroid scan, made us think of an extrathyroidal source of thyroid hormone secretion. Low thyroid radioiodine uptake and scintigraphic faintly visualized thyroid tissue in patient 2, along with negative antibodies, excluded the diagnosis of either Graves' disease or nodular toxic goiter, which is the most common association with DTC.

As both thyrotoxicosis and metastatic DTC increase the morbidity and chances of mortality the therapy should be aimed at treating both thyrotoxicosis and metastatic disease.[1] As the metastatic disease is often large, bulky, and extensive in such patients with thyrotoxicosis, the usual routine doses of beta blockers and anti-thyroid drugs are not useful in controlling the symptoms. High doses of anti-thyroid drugs such as carbimazole 60 mg daily and propranolol 40 mg every eight hours are required. Even after treatment with antithyroid drugs, hyperthyroidism is not fully controlled in and prompt clinical recovery can usually be achieved by radioiodine therapy.[3]

The same management was done in both patients and no ill effects were observed after radioiodine therapy. Patient 1 became hypothyroid after a single dose and patient 2 became euthyroid after the third dose and hypothyroid after the fifth dose and both are still under follow up.

Guglielmi *et al.* reported a case of thyrotoxicosis caused by a huge and surgically unresectable liver metastasis from follicular thyroid cancer, unresponsive to treatment, with large doses of thionamides. The combination of percutaneous interstitial laser photocoagulation treatment and radioiodine therapy made possible the effective management of a hyperfunctioning and surgically untreatable liver metastasis from thyroid follicular carcinoma, avoiding the side effects of ^{131}I therapy in a thyrotoxic patient and increasing the effectiveness of radioiodine-induced neoplastic tissue ablation.[6] Salvatori *et al.* reported severe thyrotoxicosis due to functioning pulmonary metastases of well-differentiated thyroid cancer.[1]

Thyrotoxicosis due to functioning metastatic follicular thyroid carcinoma after twelve ^{131}I therapies was reported by Tan *et al.* in which the thyrotoxicosis resolved only after surgical excision of a pelvic lesion.[7] Haq *et al.* reported a case of a 54-year old male presenting with thyrotoxicosis due to functioning pulmonary metastasis from differentiated thyroid cancer effectively treated by ^{131}I therapy.[3] Faivre *et al.* reported two cases of thyrotoxicosis, revealing functional metastases of a follicular carcinoma that extended to the bones, liver, and kidneys in one case and to the lungs in the other. Iodine-131 therapy was effective at suppressing the thyrotoxicosis in both the patients.[8] Sundaraiya *et al.* reported a case of metastatic thyroid cancer diagnosed on a technetium ^{99m}Tc- pertechnetate thyroid scan.[9]

An interesting concept called the flip-flop phenomenon has been recently reported. It reflects differences in tumor cell differentiation. Feine *et al.* studied the relation between ^{131}I uptake and FDG uptake in 41 patients of metastatic differentiated thyroid cancer. Combined ^{18}FDG and ^{131}I imaging resulted in a sensitivity of about 95%, with alternating uptake of ^{131}I and ^{18}FDG in the metastases: ^{131}I trapping metastases with no ^{18}FDG uptake and ^{18}FDG trapping metastases with no ^{131}I uptake.[10] Subsequently, in a review of 222 patients who had undergone both ^{131}I WBS as well as FDG PET he found the sensitivity and specificity of 75% and 90% for FDG PET. He also explained that cancers with good differentiation were better imaged with ^{131}I, and those with poor differentiation being better imaged on PET scan.[11] Rodrigues *et al.* studied ten radioiodine negative patients and found a 'flip-flop' phenomenon between ^{99m}Tc-depreotide and ^{18}F-FDG-PET in one patient.[12] A combination of ^{18}FDG and ^{131}I whole-body imaging protocol enabled the detection of local recurrence or metastases on whole-body scans that were often not shown by other imaging methods.

Biochemical grading of thyroid cancer may also be possible with this method: Tumors with good functional differentiation for hormone synthesis and iodine uptake have low glucose metabolism in more than 95%; tumors without this functional differentiation of ^{131}I uptake show high glucose metabolism. ^{18}F-FDG uptake seems to be an indicator of poor functional differentiation, and possibly more aggressive malignancy, in thyroid cancer.

Patel *et al.* described this flip-flop phenomenon in two contrasting cases of lung metastases from thyroid cancer illustrating the growing role of FDG-PET scans in the evaluation and management of patients with thyroid carcinomas.[13] Zettinig *et al.* reported ^{18}F-FDG PET, ^{99m}Tc-MIBI, and radioiodine imaging features in a 63-year-old

patient with metastatic insular thyroid carcinoma. He reported the 'flip-flop phenomenon' in insular thyroid carcinoma, and an alternating pattern of metastases with either ^{131}I or FDG uptake. Despite the poorly differentiated histologic findings, glucose metabolism was not increased in this patient with an insular tumor.[14]

In case 1, FDG-PET showed high uptake in the bony lesions, while the pulmonary lesions did not. Thus, the flip-flop phenomenon was seen in the lung lesions, but not in the bony lesions. Such an occurrence may be due the variable differentiation in the varied metastatic lesions.

The two cases mentioned above highlight the utility of whole body pertechnetate scintigraphy in thyrotoxic patients, with abnormal foci of uptake on a routine thyroid scan and provides us the impact of correct diagnosis for appropriate treatment, which aims at resolving the thyrotoxicosis and in treating the metastatic disease.

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