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Detection of Functioning Thyroid Cancer Metastasis on Whole Body Pertechnetate Scintigraphy.

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ABSTRACT
Thyrotoxicosis due to functioning metastases in differentiated thyroid cancer (DTC) is exceedingly rare. It may constitute confusing diagnostic as well as present therapeutic challenges. We present here two patients, a discussion and literature review on the subject. The patients presented initially with thyrotoxicosis and on routine 99mTc pertechnetate thyroid scan extrathyroidal foci of uptake were found, subsequently leading to the diagnosis of metastatic thyroid cancer. Histology showed both cases as follicular thyroid carcinoma. In one patient 18F-FDG displayed the metastases despite these foci exhibiting iodine avidity at an earlier 131-I diagnostic scan. Both patients later received radioiodine in therapy doses. One patient had a pre-therapy total thyroidectomy. The other did not because of a relapse of his thyrotoxicosis even though he had been vigorously treated with anti-thyroid drugs. He received 131-I therapy as palliation. Both patients are doing well on thyroxine replacement in suppressive doses and are being followed up. TC-99m pertechnetate whole body scan is showed here as useful in the detection of functioning distant metastases from differentiated thyroid carcinoma although 131-I Whole Body Scan (WBS) is still generally considered the method of choice.
Key words: Differentiated thyroid cancer, functioning metastases, pertechnetate whole-body scan.

INTRODUCTION

This article presents, together with a discussion and literature review, two cases of patients with thyrotoxicosis due to functioning metastases from thyroid cancer. Thyrotoxicosis due to functioning metastases from thyroid cancer is a rare occurrence with about 72 cases reported in literature[1-15]. This entity presents challenges for both the diagnostic evaluation and choice of therapeutic strategy when compared with the much more common non-hyperfunctioning metastasis from thyroid cancer[9]. Radioactive Iodine Uptake (RAIU) test and 99mTc pertechnetate scan are investigations routinely employed in the clinical investigations of thyrotoxic patients. These have been employed in the evaluation of our patients. In addition to these, 18-F-fluoro-2-deoxyglucose positron emission tomography with computerized tomography (^{18}FDG PET CT) was used. The role of ^{18}FDG PET in thyroid cancer is getting established, not only in localizing distant metastasis where there is no ^{131}I uptake[15-19], but also aiding the understanding of tumor biology important in selecting treatment options and for determining prognosis[20].

Case 1: A 65year old male patient presented to the *All India Institute of Medical Sciences department of Nuclear medicine* for evaluation of thyrotoxicosis. It was discovered from history that patient was thyrotoxic for the preceding 6 months and was being treated with anti-thyroid drug carbimazole 5mg tds. Four months into his treatment however, he developed a right sided thyroid nodule. Fine needle aspiration cytology (FNAC) of this nodule was reported as follicular neoplasm. He subsequently underwent a near total thyroidectomy. Histopathology of thyroid specimen revealed a follicular carcinoma in the right lobe co-existing with adenomatous goiter in the left lobe. Two months post surgery, patient again developed thyrotoxic symptoms and was referred for pertechnetate thyroid scan. Evaluation of results revealed minimal uptake in the thyroid bed as well as intense tracer concentration in left shoulder. A pertechnetate whole-body scan was therefore done at the same sitting to explore any other site of uptake, and

this indeed revealed uptake foci in both lung fields and pelvic bones bilaterally. A 1.2mCi ^{131}I whole-body scan further confirmed the above sites of uptake: 0.6% in the anterior neck and 7% over the left shoulder at 24 hours. An ^{18}FDG PET CT scan was in addition done revealing few pulmonary foci while confirming the bony lesions in the left shoulder and pelvis. Based on the findings of thyrotoxicosis with multiple pulmonary and bony metastases, patient was admitted for high dose radioiodine therapy. Pre-radioiodine biochemical examination was in toxic range (T3, 430ng/dl; T4, 15.3µg/dl; TSH, 0.03IU/L). An oral dose of 143mCi ^{131}I was administered to the patient. Radiation monitoring at one meter (1m) was done daily and patient was discharged when the reading dropped to less than 3mR. Post therapy scan done on discharge showed radioiodine concentration in the same lesions as above. No new ones were seen. Patient returned after 6 months for follow up and the next dose of radioiodine. At this time he had become hypothyroid (T3, 98ng/dl; T4, 4.5µg/dl and TSH 18IU/L). He was placed on 150µg thyroxine daily which he continues to take till date.

Case2: A 62 year old male farmer presented to the medical out patient department of the same hospital with chief complaints of breathlessness, bilateral chest pain and intermittent fever since 3 months. He had a past history of pulmonary tuberculosis diagnosed 2 years previously for which he had received a 6 month course of anti-tuberculosis drugs. On examination he was found to be tachycardic (pulse rate of 110/min) and with a respiratory rate of 24/min; arterial blood pressure was normal. Also noted were swellings of the left 7th to 10th ribs posteriorly. Patient exhibited thyrotoxic symptoms and so his T3, T4 and TSH were assayed. Thyroid profile was indeed found to be in toxic range with TSH being undetectable while anti-thyroid peroxidase (anti TPO)and anti-thyroglobulin (anti-Tg) antibodies were negative. Patient was referred to the department for RAIU test and pertechnetate thyroid scan. The 2hr and 24hr uptake values were 1% and 0% respectively. Pertechnetate thyroid scan revealed no uptake in the region of the thyroid but foci of intense uptake were seen in the skull and left shoulder.
A decision to do a whole-body pertechnetate scan at the same sitting was made and this showed multiple foci of intense tracer uptake in the ribs bilaterally, including a large focus extending laterally from the 7th to the 10th left ribs. In addition a focus of uptake was seen over the sternum while multiple hot spots were also found in the pelvis and sacrum. A suspicion of possible metastatic thyroid cancer was entertained. Subsequently, patient underwent an ultrasound-guided fine needle aspiration biopsy from the left side chest wall lesions. Examination of the biopsy specimen revealed thyroid follicular cells. Immunohistochemistry of the aspirated specimen returned a positive result for thyroglobulin, focally positive for CK19 and negative for TTF1. Patient underwent CT chest, skeletal survey and X-ray of the thoraco-lumbar spine and these among other things revealed lytic bone lesions consistent with multiple chest wall and vertebral (L5-S1) metastases. Subsequently, the patient had a neck ultrasound scan which showed multiple heteroechoic lesions in both lobes of the thyroid gland including a large solid nodule in the lower part of the left lobe. Ultrasound-guided FNAC was here done and the aspirate samples examined. A diagnosis of follicular neoplasm was returned. The patient was started on carbimazole 15mg tds and propranolol 40mg bd to control the thyrotoxic symptoms. The patient's thyroid profile improved on these drugs from 5.93/24/UD to 1.5/11/0.35 within three weeks only to worsen again to 6.2/24.5/UD over the next 2 weeks. Patient was deemed to be a poor candidate for surgery due to his age and unpredictability of his thyroid function. A decision to give radioiodine therapy as palliation for the metastases was taken and patient subsequently received 100mCi of ^{131}I. Serial monitoring showed excellent whole-body retention and patient was discharged only after 7 days. A post therapy whole body scan corroborated the findings of the pre- therapy scans with no new lesions detected. Four weeks after the radioiodine therapy his profile improved to 3.79/20.4/0.01 and he admitted improvements in his symptoms of thyrotoxicosis and chest pain. At present the patient apart from the thyroid replacement is also on carbimazole 15mg tds and propranolol 20mg tds. He has been planned for a repeat assessment for thyroidectomy, which if contraindicated; a

repeat palliative radioiodine will be given.

DISCUSSION

Extra-thyroid Thyrotoxicosis resulting from or associated with metastatic thyroid cancer is rare. Hyperthyroidism can be severe, and as seen in our patients, often T3 levels are markedly more elevated than T4[21]. The most common association is the incidental coexistence of Graves disease[22] and well differentiated thyroid cancer; only very rarely is the association due to functioning neoplastic tissue[23]. The first case of this syndrome was described in 1946 by Leiter *et al*. and the characteristics were reviewed by Sisson[24]. The importance of this phenomenon lies in the resultant diagnostic as well as the therapeutic challenges of managing the thyrotoxicosis and curing the neoplastic disease[9]. Thyroid carcinoma and its metastases are usually shown as photopoenic defects on scintigraphic images with radioiodine and/or Tc-99m pertechnetate but several cases showing an accumulation of radioiodine and/or pertechnetate in thyroid carcinoma[25,26,27] and/or in its metastases[28-34] have been described. I-131 and Tc-99m pertechnetate commonly do not show signs of accumulation in thyroid carcinoma and/or its metastasis except in a few cases[25-34].

The two patients we present were found at presentation with thyrotoxicosis due to functioning pulmonary and skeletal metastases from follicular carcinoma. This similar situation has been reported by other workers[1,24]. Similarly, others have described cases with thyrotoxicosis presenting without dysthyroid eye disease in the presence of metastatic disease[1,9,24]. In addition, the exclusion of a hyper-functioning diffuse or nodular thyroid gland, demonstration of radioiodine uptake by metastatic lesions, low thyroid radioiodine uptake and failure of thyrotoxicosis to resolve after adequate thyroidectomy have been used as criteria for making a diagnosis of extra-thyroidal thyrotoxicosis[35]. Our two patients fulfilled these criteria although as seen from the history and Table 1, the second patient is yet to be offered a thyroidectomy because the relapse of his thyrotoxicosis despite vigorous anti-thyroid drug therapy initially made him a poor candidate for surgery. His thyrotoxicosis was and has so far remained controlled after a single therapy dose (100mCi) of radioiodine 131. The success of his treatment can also be contributed to by the vigorous pretreatment with anti-thyroid drugs. Salvatori *et al*[9] reported a similar experience.

It will be noted that our patients presented with a large tumor burden as can be seen from the multiplicity of metastatic foci and the intensity of the uptake at the pertechnetate thyroid and whole body scans (WBS). In differentiated thyroid carcinoma (DTC), whole body I-131 scintigraphy is the method of choice for the detection of metastatic lesions with a positive rate of approximately 75%[34]. Only 1% of DTC patients are reported to concentrate Tc-99m pertechnetate[37], and for this small percentage of tumors it has been postulated that they have the ability to concentrate pertechnetate because they retain their anion trapping mechanism[38]. Paradoxically patient 2 showed no tracer concentration in the thyroid while exhibiting activity in the metastases. This may be due to dedifferentiation of the thyroid cancer. In the first patient, the iodine-avid metastases were also demonstrated by the subsequent FDG PET/CT scan. Using FDG-PET imaging, Feine *et al*[20] noted that differentiated tumors with iodine avidity have low glucose metabolism in most patients, with the converse being true (flip-flop phenomenon), indicating that high glucose metabolism (enhanced expression of glucose transporter genes- GLUT and loss of sodium-iodide symporter activity) signifies poor tumor differentiation and higher possible malignant potential[39-41]. Furthermore the PET-FDG standard uptake value (SUV) is a strong predictor of adverse prognosis, with higher SUV's indicating worse overall prognosis[42]. In the patient we present we found that his primary and metastases were both iodine and FDG avid. This may suggest that tumor de-differentiation exists as a wide spectrum, with our patient being somewhere in the middle: losing some degree of iodide symporter potential yet capable of iodine concentration and acquiring enough GLUT activity to confer reasonable FDG avidity.

Conclusion

In conclusion, pertechnetate whole body scan is useful in the detection of functioning distant metastases from differentiated thyroid carcinoma although 131-I WBS is still considered the method of choice. Some iodine avid thyroid

cancers and/or their metastases may also be glucose-avid and be demonstrated on ^{18}F- FDG-PET CT scans despite the existence of the flip-flop phenomenon. In thyrotoxic patients considered poor candidates for thyroidectomy, high dose radioiodine can be safely deployed after vigorous pretreatment with ATDs.

Table 1 Comparison of some of the clinico-pathological aspects in both patients. ND Not done

Clinico-pathological Indices	Patient 1			Patient 2		
Age (Years)	65			62		
Sex	Male			Male		
Presentation	Thyrotoxicosis, thyroid nodule			Thyrotoxicosis, chest pain, fever		
FNAC	Site	Diagnosis		Site	Diagnosis	
	Thyroid	Follicular neoplasm		Chest wall	Follicular cells	
				Thyroid	Follicular neoplasm	
Surgery	Total thyroidectomy			ND		
Tc-99m thyroid scan	Thyroid bed^{+}, Left shoulder^{+++}			Thyroid bed^{-},skull^{++}, left shoulder^{++}		
Tc-99m WBS	Lungs$^{++,}$ Pelvis^{++}			Ribs^{++}, sternum^{++}, pelvis^{++}, sacrum^{++}		
RAIU(24h)	0.6%(neck), 7%(left shoulder)			0% (neck)		
^{18}FDG PET/CT	Lungs^{+}, shoulder^{+}, pelvis^{+}			ND		
^{131}I Therapy Dose	143mCi			100mCi		
Pre^{131}I R$_x$ Thyroid Profile	T3ng/dl	T4µg/dl	TSHIU/L	T3	T4	TSH
	430	15.3	0.03	6.2	24.5	UD
Post ^{131}I R$_x$ Thyroid Profile	T3	Therefore	TSH	T3	T4	TSH
	98	4.5	18	3.79	20.4	0.01
Thyroid Ultrasound	ND			Heteroechoic lesions, large solid nodule		
X-ray/CT	ND			Lytic metastases in ribs, LS-spine(L5-S1)		
Immunohistochemistry	Tg	CK-19	TTF-1	Tg	CK-19	TTF-1
	ND	ND	ND	+ve	+ve	-ve
Final Histological diagnosis	Follicular cancer (right lobe), adenomatous goiter (left lobe)			Follicular cancer		
Comments	Relapse of thyrotoxicosis post thyroidectomy			Relapse of thyrotoxicosis post ATD, controlled after palliative radioiodine therapy		
Outcome	Stable disease			Stable disease, awaiting reassessment for possible thyroidectomy		

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