Case report

^{111}In–pentetreotide scintigraphy and 18F FDG PET–CT in differentiated thyroid carcinoma metastases with negative whole body radioiodine scan

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Abstract

Metastases of differentiated thyroid cancer (DTC) can lose affinity to radioiodine with the passage of time, with resultant difficulty in management. Thyroid tumors are known to express somatostatin receptors and therefore ^{111}In–pentetreotide, somatostatin analogue, can visualize tumors with high concentration of somatostatin receptors. We report a case of I–131 whole body scan (WBS) negative recurrent metastatic papillary thyroid carcinoma with positive 18F FDG PET–CT and ^{111}In–pentetreotide scan. Somatostatin receptor scintigraphy (SRS) with ^{111}In–pentetreotide may be useful both in the staging and monitoring of patients with non–iodine avid carcinoma of the thyroid. ^{111}In–pentetreotide scan positive patients are potential candidates for somatostatin receptor–targeted therapy.

Keywords

Differentiated thyroid cancer, ^{111}In–pentetreotide scintigraphy, somatostatin receptor–targeted therapy.

Introduction:

After initial treatment of differentiated thyroid carcinoma (DTC), patients are routinely followed–up using serum thyroglobulin (Tg) measurement and conventional I–131/123 scintigraphy. [1,2] Tumor recurrence occurs in about 20% of patients and is associated with significant morbidity and even mortality. [3,4] Whenever recurrence or metastatic disease is evident on the whole body iodine scan (WBIS), patients are retreated with radioiodine. However, in 20%–30% of patients, additional Iodine 131 therapy is not effective because of the lack of radioiodine uptake in tumors. Patients with elevated thyroglobulin levels, but no identifiable focus of disease on WBIS, pose a therapeutic and diagnostic dilemma. [5] Further surgery and external beam radiotherapy is the mainstay of management for these patients due to poor response to chemotherapeutic agents.

Morphologic imaging modalities such as sonography, CT, and MRI may be effective in localizing lesions that have failed to concentrate Iodine 131, especially in the case of local recurrences, but these modalities are not practical for whole–body evaluation. Further, they often cannot be used to distinguish active disease from the fibrotic residue of previously treated disease. 18F–Fluorodeoxyglucose–positron emission tomography (18F–FDG PET–CT) imaging is able to detect poorly differentiated metastases and is considered an important diagnostic tool in localizing radioiodine negative thyroid cancer. [6,7]

Papillary and follicular thyroid cancer have been found to overexpress somatostatin receptors (SSTRs) 3, 4, and 5 [8,9,10] and several reports have demonstrated uptake of ^{111}In–pentetreotide in metastatic or recurrent disease. [11,12,13] This offers the possibility of somatostatin receptor scintigraphy (SRS) and targeted therapy in patients with elevated serum thyroglobulin levels but no

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evidence of disease on radioiodine scintigraphy. We report on a case of histologically proven nodal and lung metastasized papillay thyroid carcinoma with elevation of serum Tg, and a negative I–131 WBS in whom the management was critically informed by [111]In–pentetreotide scintigraphy and 18F FDG PET–CT.

Case Report

A 36–years old male patient presented in March 2007 with a three month history of swelling on the left side of his neck which was found to be secondary to supraclavicular lymphadenopathy. FNAC from nodes demonstrated metastatic papillary carcinoma thyroid. Total thyroidectomy and excision of left supraclavicular lymph nodes with selective dissection of internal jugular chain lymph node was done. Histopathology of both thyroid lobes showed foci of papillary carcinoma with capsular and vascular invasion. No skeletal muscles were involved and 6/7 nodes showed metastatic carcinoma with extranodal extension.

Post operative WBIS scan was done in April 2007, which showed residual uptake in the thyroid bed of about 2.3%. Patient received an ablation dose of 84mCi in May 2007. Post ablation scan was unremarkable. He was put on 150µgm of Eltroxin daily and followed up with thyroid function test and Tg.

In December 2012 he noticed swelling in his lower left neck. Routine chest radiograph showed a right lung lesion. CT scan of neck and chest showed a pleural based lesion in the right lower lobe, multiple bilateral pulmonary nodules and numerous enlarged lymph nodes with central calcification seen in the cervical, supraclavicular, mediastinal, subcarinal and hilar stations. Biopsy of pleural mass and left supraclavicular nodes showed metastatic papillary carcinoma of thyroid.

Iodine 131 WBS was done after post thyrogen injection, which showed minimal uptake in the thyroid bed of approximately 3.6%. Very faint doubtful uptake was seen in the left supraclavicular region (Figure 1). Tg was elevated (5590ng/ml) and increased further after thyrogen administration (6616 ng/mol – Reference range <10.0ng/ml).

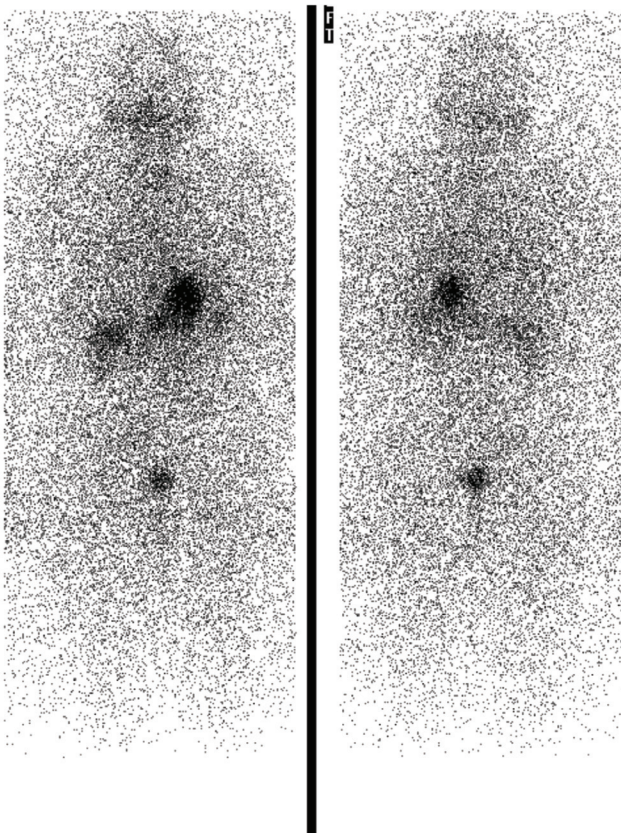

Figure 1: 131 Post Thyrogen Whole body scan with 3mCi show minimal uptake in the thyroid bed with uptake of 3.6%. Very faint doubt full uptake is seen in the left supraclavicular region. Tg is very high at 5590ng/ml and post thyrogen is 6616 ng/mol (reference range <10.0ng/ml)

[18]F FDG PET–CT scan showed hypermetabolic thyroid tissue (SUV 16.1), with multiple FDG avid lesions in the right lower cervical (SUV 7.1), supraclavicular (SUV 13.1), left parasternal (SUV 5.1), right paratracheal (SUV 11.1), right hilar (SUV 11.2), and subcarinal nodes (SUV 16.9). Further hypermatabolic lesions included two pleural based lesions in the right upper and lower zones and a right lung parenchymal lesion (Figure 2).

In view of negative Iodine 131 WBS, [111]In–pentetreotide scintigraphy was also performed which showed increased tracer uptake in most of the lesions identified on FDG PET–CT including; anterior mediastinum, supraclavicular and posterior basal right thoraccic lesion (Figure 3). Thus, the patient became a potential candidate for octreotide therapy.

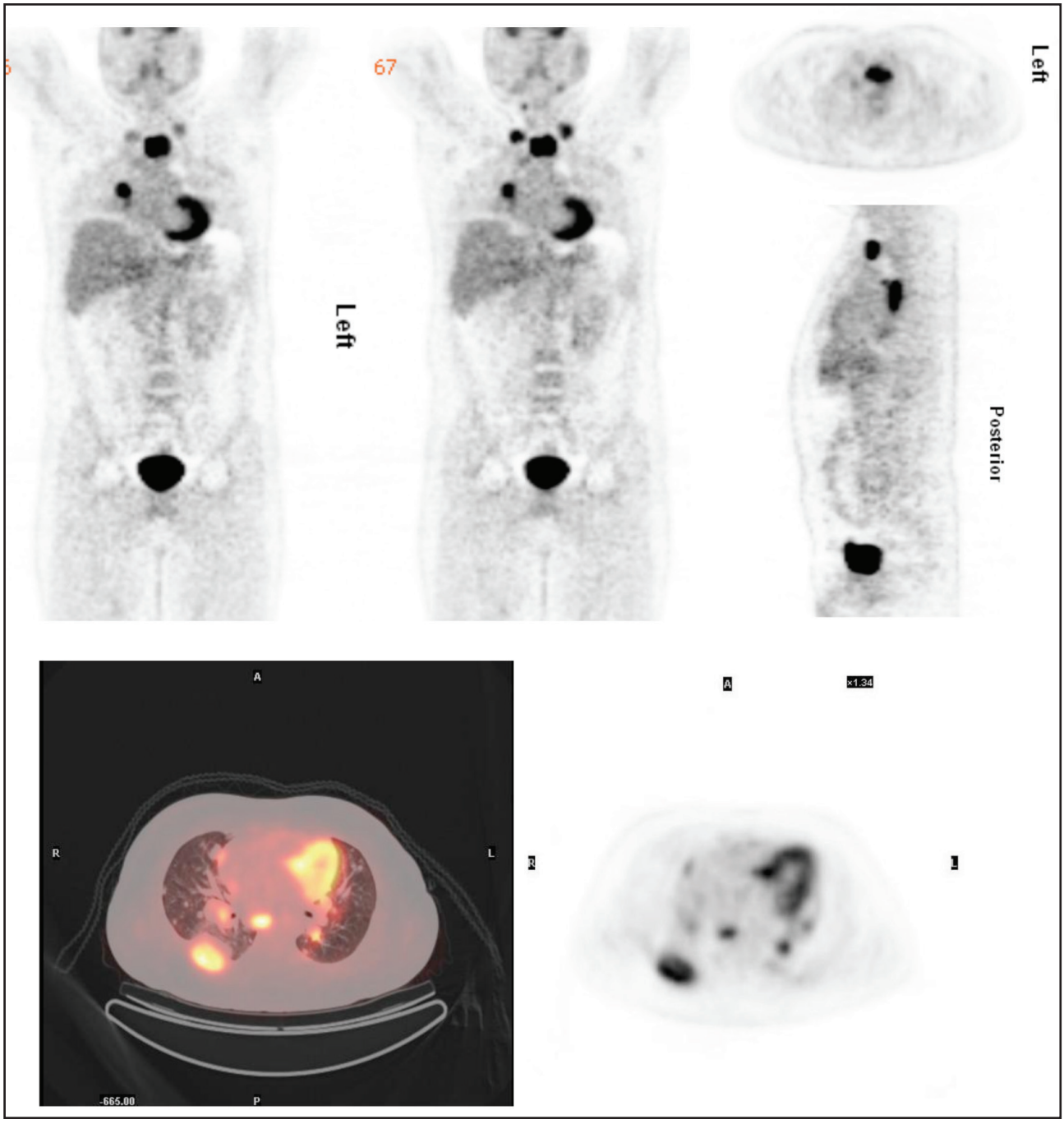

Figure 2: 18F FDG PET/CT scan show multiple hypermetabolic FDG avid lesions at right lower cervical, bilateral supraclavicular, hypermetabolic remnant thyroid tissue, left parasternal, right paratracheal, right hilar, subcarinal, two pleural based lesion at right upper and lower lobe and parenchymal lesion at right lung.

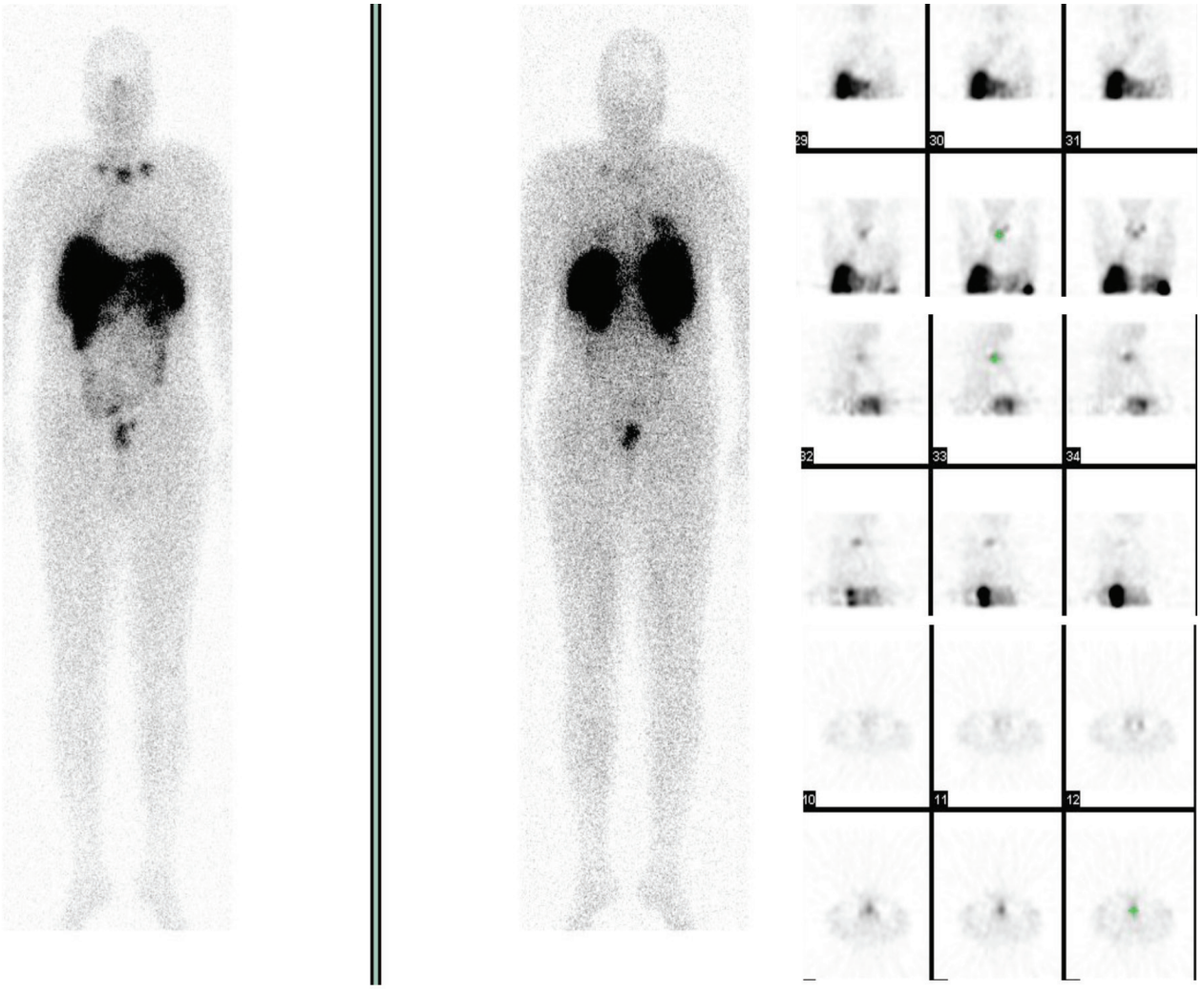

Figure 3: 111In–pentetreotide whole body images and SPECT images of the chest shows focal areas of increase tracer uptake at bilateral supraclavicular region, anterior mediastinum. Focal areas of increase tracer uptake are also seen at right chest.

Discussion

Up to one–third of metastasized or recurrent thyroid carcinomas may dedifferentiate over time. This is characterized by a loss of growth–regulating mechanisms mediated by TSH and/or a decline in iodine avidity making them eventually inaccessible to radioiodine therapy. [14] This effect is commonly attributed to lost or reduced expression of the thyroidal sodium/iodide symporters.

I–131 whole body scanning and serum Tg level monitoring, both under TSH stimulation (either by withdrawal of thyroxine or exogenous thyrotropin administration) is the preferred method for routine follow–up of DTC. [15] Increase in Tg under TSH stimulation is considered the most reliable indicator of persistent or recurrent disease, with 98% sensitivity[16] In cases of increased Tg levels but negative WBIS, restaging is accomplished by using other diagnostic imaging modalities. Several studies have investigated the role of ^{18}F FDG PET–CT in detecting recurrent or metastatic DTC. [17,18,19,20] 18F FDG PET–CT is at present the best reference imaging study in evaluation of DTC patients with negative Iodine 131 WBS and elevated Tg levels as well as in cases of undetectable Tg with clinical suspicion of recurrence or metastases. ^{18}F FDG PET–CT has demonstrated clinical utility in evaluating non–iodine–avid lesions, with sensitivity approaching 90%. [21,22] This peculiar phenomenon has been described by Feine et al [23] as the "flip–flop" mechanism, where the dedifferentiated tumors lose iodine trapping capability, but have increased glucose metabolism and vice versa.

Dedifferentiation of DTC, apart from manifesting disappearance of the iodine–uptake properties, may also lead to tumor tissue overexpression of hSSTR, suggesting that radiolabeled hSST analogues may constitute useful means for detecting I–131–negative metastases. A series of studies have been performed showing that 74% of differentiated thyroid cancers have uptake of ^{111}In–pentetreotide including some cases which were negative on 18F FDG PET–CT. [24,25] The expression of SSRTs on the target tissue constitutes the basis of somatostatin receptor scintigraphy. Baudin et al. were the first to report on the use of 111In–pentetreotide scintigraphy in DTC. [26] An overall sensitivity of 80% was described, irrespective of the WBIS result. [27] Gorges et al. and Postema et al. [25] reported positive correlation between sensitivity of SRS and the Tg levels.

Therapeutic options in patients with recurrent or metastatic DTC that cannot concentrate radioiodine are limited. Also, the loss of iodine–trapping ability, or dedifferentiation, is associated with a more aggressive behavior. Peptide Receptor Radionuclide Therapy (PRRT) with radiolabelled somatostatin analogues is a promising treatment option for patients with Iodine 131 scan negative, but thyroglobulin positive DTC. ^{111}In, ^{90}Y, or ^{177}Lu–labelled somatostatin analogues have been used. At present therapeutic efficacy of PRRT in patients with non–radioiodine–avid or unresponsive thyroid cancer is difficult to assess as the number of treated patients in studies reported so far are limited and there is variability of administered doses and the use of different types of radiolabeled somatostatin analogs. [28] A pilot study of eight patients with radioiodine resistant, DTC treated with Yttrium–90–labeled octreotide (DOTATOC) showed that thirty–five percent of the patients demonstrated stable and 65% progressive disease[29] A recent publication using the same agent but with a different dosing protocol assessed 24 patients with DTC resistant to radioiodine therapy. Seven patients (29.2%) demonstrated a decrease in thyroglobulin levels (median reduction 48.9%). Median follow–up was 14.9 months, and an increased survival time from diagnosis was described. [30] 177Lu–DOTATATE therapy can also be effective in patients with progressive DTC who have no therapeutic options and sufficient uptake of 111In–octreotide in tumor lesions. [31]

In our case the patient had a positive ^{18}F FDG PET–CT and ^{111}In–pentetreotide scans. Surgery was not a viable option because of widespread dissemination of the disease. ^{111}In–pentetreotide avidity allowed consideration of somatostatin receptor–targeted therapy. The dedifferentiation of thyroid carcinoma resulting in sequential loss of function, including loss of iodine trapping and loss of somatostatin receptors with increase in glucose metabolic activity makes a combination strategy of utilizing both SRS and PET–CT imaging for assessment of non–iodine–avid lesions a feasible option in these patients. Those patients with a high proportion of somatostatin–receptor–avid lesions may benefit from PRRT. [34] While those with solely FDG–avid lesions could potentially benefit from novel chemotherapy agents such as Sorafenib™. [32] This case has offered us a unique opportunity to revisit the treatment of non–radioiodine avid, differentiated thyroid cancer. It is our hope that the discussion will encourage new studies to further evaluate the use of somatostatin receptor scintigraphy as a diagnostic tool for both staging and monitoring of disease in these patients.

Conclusions

Imaging with ^{111}In–pentetreotide may be useful both in the staging and monitoring of patients with non–iodine avid carcinoma of the thyroid. Tumor that has been identified may be surgically resectable and could result in increase survival rates. For unresectable disease, SRS positive patients may progress to somatostatin receptor–targeted therapy.

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