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Case Report Open Access

Follicular Thyroid Carcinoma: A Tumor Histotype that Should Not be Underestimated

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Abstract

Papillary and Follicular Differentiated thyroid carcinoma have a very good prognosis, such that survival in low-risk forms is comparable to a healthy person. However, the follicular thyroid carcinoma is typically more aggressive than the papillary one, so that in some patients the distant metastases represents the first clinical manifestation of the disease.

Although this is a rare condition, we can find asymptomatic distance metastases in the 18F-FDG PET/CT as "incidentalomas", even in the absence of a primary tumor. This condition could be incorporated into the term occult thyroid carcinoma.

In patients with iodine avid metastatic differentiated follicular thyroid cancer, even if some metastatic lesions show pathological hypermetabolism to the 18F-FDG PET/CT scan, radioactive iodine therapy remains the treatment of choice. In this setting of patients the dosimetric study is mandatory.

Keywords: Follicular thyroid carcinoma; 18F-FDG PET/CT scan; Differentiated thyroid carcinoma; 18F-FDG PET/CT incidentalomas; Occult thyroid carcinoma; Radioactive iodine treatment; Dosimetric study

Introduction

Follicular thyroid carcinoma (FTC) is tipically a solitary encapsulated tumor that may be more aggressive than papillary carcinoma. It is identified as cancer by follicular cell invasion of the tumor capsule and/or blood vessels [1].

The lung is the most common metastatic site for thyroid carcinoma followed by bone [2]. As recently reported, distant metastasis as the sole initial manifestation of well-differentiated thyroid carcinoma (WDTC) is rare and follicular thyroid carcinoma was most common [3]. Even rarer is the detection of distant metastasis from an occult FTC.

Here, we report a rare case with iodine-avid lung, bone, adrenal metastases from an occult follicular thyroid carcinoma which was discovered after performing a Fluorine-18-fluorodeoxyglucose position emission tomography/computed tomography (18F-FDG PET/CT) scan for sarcoidosis.

Pre-therapeutic dosimetry before RAI (radioactive iodine) treatment was made for calculation of maximum tolerated activity of ^{131}I.

^{131}I WBS (whole body scan) post-therapy with SPECT/CT scan has allowed to highlight focal radioactive iodine uptake even in anatomic sites that are atypical for metastases such as the skull, the brain and the soft tissues of the mandibular region.

Case Presentation

A 71-year-old woman arrived at our Nuclear Medicine Department on December 2018 with diagnosis of FTC metastases to undergo Radiometabolic Therapy with ^{131}I. The patient underwent total thyroidectomy in April 1996 due to the presence of multinodular goiter.

The histological examination highlighted-"Thyroid (right lobe): plurinodular struma. Left lobe: follicular adenoma with regressive areas. In the surrounding, thyroid parenchyma aspects referable to struma are observed".

The patient had a history of pulmonary sarcoidosis. On March 5, she was referred to our Nuclear Medicine Department for 18F-FDG PET/CT scan for the follow-up of the known disease.

The study showed the presence of pathological hypermetabolism in correspondence of an infiltrating formation of the posterior arch of the XI left rib and of the left cost-vertebral articulation (SUVmax 3.73).

Similar pathological findings at the V, VI and VII right ribs were detected. Another expansive hypermetabolic lesion was located in the right adrenal gland (Figure 1).

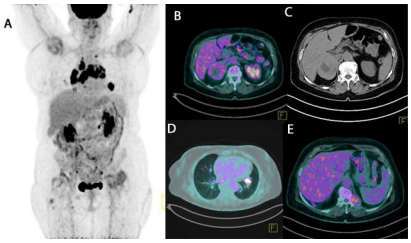

Figure 1: 18F-FDG PET/CT findings-MIP (maximum intensity projection) imaging (A); Right adrenal gland with hypermetabolism (SUV Max 8.41) (B); expansive lesion on CT (C); Focal hypermetabolic pulmonary nodular formation at the left lower lobe (SUV max 20.35) with multiple bilateral pulmonary nodulations (D); Increased activity of the posterior arch of the XI left rib and of the left cost-vertebral articulation (E).

Moreover 18F-FDG PET/CT imaging revealed also a lymph node hypermetabolism in right paratracheal, left para-aortic, at the level of the carina and at the bilateral hilar pulmonary region and also at multiple bilateral pulmonary nodulations. A focal hypermetabolic pulmonary nodular formation at the left lower lobe was also observed.

Contrast enhanced CT Scan (CECT) confirmed the findings highlighted to PET/CT and posed the suspicion of a repetitive hepatic lesion. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) of lymph node (Station 7) was performed. The cytological examination showed: "Mostly mucohematic material incorporating some macrophages and cylindrical cells sometimes artefacts both scattered and forming some aggregates. Research into neoplastic cells in the test material was negative".

The patient underwent CT-guided right adrenal biopsy. The histological examination depicted metastasis of follicular thyroid neoplasia. Thyroglobulin levels were elevated (Tg 2120 ng/ml) while Thyroglobulin antibodies were within normal limits. Thyroid stimulating hormone (TSH) was 3.04 microU.I./ml.

A complete revision of slides was performed. It recited: "Thyroid (left lobe): "In the only claim received: Thyroid follicular proliferation not further definable. The lesion is capsulated, and shows focal areas suggestive, but not fully conclusive, for tumor necrosis. Note: review of all the histological preparations set up in the case may be useful. Needle biopsy adrenal: Adrenal localization of well-differentiated thyroid follicular carcinoma. Immunohistochemical stainings performed: positivity of neoplastic cells for PAX8, TTF-1 and Thyroglobulin".

On August 24, the patient was subjected to radioguide surgery to remove pre-thyroid tissue and a right para-thyroid lymph node. The histological examination showed: "Right para-thyroid lymph node: thyroid tissue with pattern of a follicular neoplasm. Immunophenotype of neoplastic tissue: HBME1 +; Cytokeratin 19 +/-; Galectin 3 -/+. Immunomorphological framework in the complex not supportive for a diagnosis of follicular carcinoma (as suggested by the disseminated thyroid neoplasia) but at the most confining a picture of an uncertain follicular tumor malignant potential ('follicular tumor of uncertain malignant potential'; FT-UMP). Pre-thyroid tissue: muscular tissue ".

The ultrasound of the neck, performed two months after the intervention, revealed small right lobe (2.11 x 0.96 x 1.29 cm) with markedly reduced echogenicity and inhomogeneous ecostructure as flogistic process and absence of nodular pathology. No secondary lymphadenopathy was observed at the submandibular, laterocervical and bilateral clavicle levels.

On December 2018, the patient was admitted into our Nuclear Medicine Department to received RAI (radioactive iodine) treatment by thyroid hormone withdrawal (her TSH was 43.39 microU.I./ml, with Tg of 11.0134 ng/ml and AbTg <3 UI/ml at the time) and a 2-week low-iodine diet. On physical examination, her blood pressure was 120/80 mmHg, with a heart rate of 78 beats/minute. The routine blood was normal. The electrocardiogram (ECG) showed sinus rhythm. The ENT visit showed a substantial bilateral cord normobility and a sufficient glottic space. She was asymptomatic.

Pre-therapeutic dosimetry before ^{131}I therapy was made for calculation of maximum tolerated activity of ^{131}I. In relation to the results of the examinations carried out, taking into account the dosimetric study and the patient's disease status, after preparation with Methylprednisolone hemisuccinate 20 mg e.v. in physiological 100 ml and Ondansetron 8 mg i.m., she was then treated with 4261MBq di ^{131}I (115,17 mCi) di ^{131}I.

The 3-day post-treatment whole body scan with SPECT/CT showed significant activity in the thyroid bed and evidence of distant metastases (Figure 2).

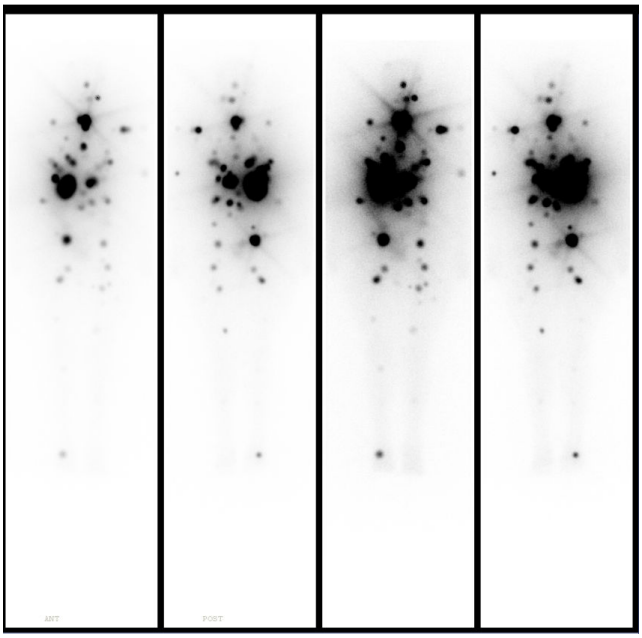

Figure 2: WBS post-RAI therapy findings: Radioiodine-avid lung, bone, adrenal metastases and radioiodine accumulation in the thyroid bed

These multiple areas of radioiodine uptake involved the lungs, the adrenal glands whit greater extension to the right, and skeletal segments. The sites of bone uptake were: the ribs, the sternal body region, the left scapula, the right acromion-clavicle region, the left humerus, the lumbar vertebrae, the pelvis with the greatest extension on the right, the femurs, the tibiae and the right malleolar region. A SPECT/CT of the cranial-cervical showed some areas of focal

radioactive iodine uptake at the parietal region of the skull, in particular at the right parietal cranial.

Three other areas of focal radiodine accumulation were showed respectively: one near the left sphenoid region, one at the soft tissue of the left mandibular region, and one at the left anterior arch of the atlas (Figure 3).

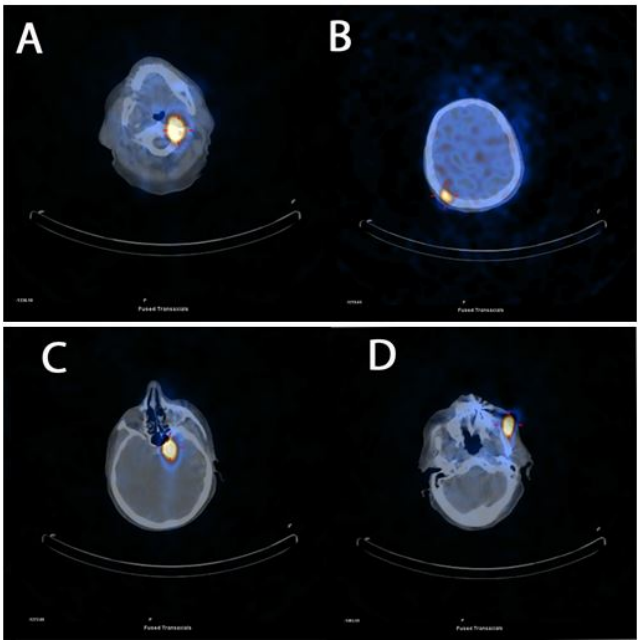

Figure 3: SPECT/CT post-RAI therapy findings-Focal radioactive iodine uptake areas respectively located: at the left anterior arch of the C1 (A); at the right parietal region of the skull (B); near the left sphenoid region (C); at the soft tissue of the left mandibular region (D).

For the latter finding, an orthopedic consultation was therefore requested. The physical examination was negative but the specialist advised to apply collar "Philadelphia" indefinitely. In the suspicion of a possible brain metastasis related to the presence of focal radioiodine accumulation near the left sphenoid region, was established therapy with Soldesam 8 mg 1 cp/day for 10 days, then to follow Soldesam 4 mg 1 cp/day for 5 days and after all suspend.

After 200 h from the ^{131}I therapeutic dose, a late Whole body scan was performed which confirmed the pathological picture without further radioiodine uptake findings. On December 14, the patient was discharged from our Department and informed of the need for a second cycle of RAI with dosimetric study after performing Magnetic Resonance Imaging (MRI) of the cervical spine and brain and neurosurgical evaluation.

Discussion

As published by Boucek and colleagues [4] "Occult thyroid carcinoma" is a general term indicating clinically different situations. The authors in fact divided "Occult thyroid carcinoma" into four different categories. The first group comprised patients with thyroid carcinoma or microcarcinoma incidentally found in the thyroid gland after total thyroidectomy for benign disease or at autopsy.

In the second group there were patients with incidentally detected papillary thyroid microcarcinoma on imaging studies, mainly ultrasonography, and evaluated by fine needle aspiration biopsy (FNAB). In these cases it could be useful to have a diffusion-weighted MR imaging of the thyroid gland [5]. The third group were patients with clinically apparent metastases of thyroid carcinoma, where the primary tumour is not detectable before surgery and microscopic tumour – microcarcinoma is found in the final histological specimen. The fourth group included patients with thyroid cancer localized in ectopic thyroid tissue with clinical symptoms or with apparent metastases.

Our case cannot be classified in these over-described categories. In fact, the presence of distant metastases was found incidentally following a 18F-FDG PET/CT performed for sarcoidosis and in an asymptomatic patient who had previously undergone total thyroidectomy for benign disease.

The association of thyroid cancer and sarcoidosis has been previously described [6]. Moreover, local lymph nodes contained sarcoidosis mixed with metastasis was detected [7]. In our case, the result of EBUS-TBNA showed no neoplastic cells and/or noncaseous epithelioid cell granulomas, typical of sarcoidosis. Coexistence of sarcoidosis and metastatic lesions is often a diagnostic and therapeutic dilemma, but in our case characterized by the presence of disseminated metastatic disease evident at the post-therapy whole body scan and at the 18F-FDG PET/CT, it did not involve particular complications in the management of the disease.

As recommended by the most recent American Thyroid Association (ATA) Guidelines [8], 18F-FDG PET scan should be considered in high risk differentiated thyroid cancer (DTC) patients with elevated serum Tg (generally >10 ng/mL) with negative RAI imaging. The 18F-FDG PET/CT imaging is indeed complementary to ^{131}I WBS, even in the presence of detectable ^{131}I uptake in metastases, because 18FDG uptake may be present in neoplastic foci with no ^{131}I uptake.

In our case the majority of bone lesions showed marked radioactive iodine uptake, with the exception of rib metastasis also obvious to the 18F-FDG PET/CT. The other metastases, in particular the adrenal and pulmonary ones, showed both radioactive iodine uptake and elevated glucose metabolism. In addition, the 18F-FDG PET/CT also showed intense hypermetabolism of the hilar and mediastinal lymph nodes, which exhibited no radioactive iodine uptake at WBS post-therapy. This condition has been related to the presence of the known inflammatory disease and confirmed by the result of the EBUS-TBNA.

The use of ^{131}I SPECT/CT also allowed to identify areas of radioiodine accumulation in sites that are atypical for metastases such as the skull and the soft tissues of the mandibular region. ^{131}I SPECT/CT was also very useful to detect the pathological involvement of the left arch of the first cervical vertebra and in locating an area of radioactive iodine uptake suspected for brain metastasis.

The precise localization and characterization of these findings is very important as it influences not only the staging and the risk stratification but, above all, the reliable clinical management of the patient. As previously demonstrated in other studies [9,10] the ^{131}I SPECT/CT improved the detection and localization of radioactive foci in the categories of lymph node and distant metastasis compared with whole-body scintigraphy and therefore, in this setting, its use is routinely recommended after ^{131}I radioiodine therapy.

This case allows us to reflect on the thyroid tumor histotype. It is known that follicular thyroid carcinoma is tipically a tumor that may be more aggressive than papillary carcinoma [1].

As described in Recommendation 48 of the ATA guidelines [8], the 2009 ATA Initial Risk Stratification System is recommended for DTC patients treated with thyroidectomy, based on its utility in predicting risk of disease recurrence and/or persistence.

It is therefore suggested to add prognostic variables, such as the extent of lymph node involvement, mutational status, and/or the degree of vascular invasion in FTC, to the 2009 ATA Initial Risk Stratification system. The patient with intrathyroidal, well differentiated FTC with capsular invasion and no or minimal (<4 foci) vascular invasion is therefore considered to belong to the Low Risk Category. Instead the patient with FTC with extensive vascular invasion (> 4 foci of vascular invasion) is considered to belong to the High Risk Category.

This classification is important to post-operative RAI decision-making. In fact in ATA Low Risk, patients did not receive RAI remnant ablation, while in ATA High Risk, post-surgical RAI is highly recommended.

Our patient presented well-differentiated FTC metastases involving the skeleton, including the skull, the lungs and the adrenal glands. Other areas with radioiodine uptake were suspected for brain and soft tissue metastases. Even if it was not possible to define from the histological examination if the primary thyroid tumor was a FTC with a number of vascular invasion foci of greater or less than 4, we consider appropriate, in the FTC, to perform RAI therapy.

Furthermore this case study, according to the Council Directive 2013/59/Euratom of 5 December 2013 [11], highlights the importance of the dosimetric study that is based on calculation of maximum tolerated activity of ^{131}I that would deliver a radiation dose to blood (considered a surrogate for the bone marrow) of 200 rad (2 Gy) or less, thus diminishing the likelihood of an adverse bone marrow effect [12]. Finally, in the era of personalized medicine and theranostic approach, this case reminds us that in patients with iodine avid metastatic differentiated thyroid cancer, RAI therapy remains the treatment of choice.

Conclusion

In the present case, patient underwent 18F-FDG PET/CT scan for sarcoidosis. The functional imaging showed intense hypermetabolism of the lungs, of the right adrenal gland, at the level of some ribs and of the right paratracheal, left para-aortic, hilar and mediastinal lymph nodes. Patient underwent EBUS-TBNA of lymph node (Station 7) that was negative for neoplastic cells. Then she was subjected to CT-guided right adrenal biopsy that highlighted localization of well-differentiated FTC. The patient had undergone total thyroidectomy, for more than 20 years, with a histological diagnosis of follicular adenoma. Despite the review of the slides and the radioguide surgery to remove pre-thyroid tissue, the primitive thyroid tumor was considered occult. Patient was asymptomatic. Patient received RAI treatment by thyroid hormone withdrawal, with dosimetric study for calculation of maximum tolerated activity of ^{131}I. The ^{131}I WBS post-therapy showed significant activity in the thyroid bed and evidence of widespread distant metastases that involved the lungs, the adrenal glands whit greater extension to the right, and skeletal segments. The ^{131}I SPECT/CT allowed to detect focal radioactive iodine uptake at the right parietal cranial, at the first cervical vertebra, at the soft tissue of the left mandibular region and another area of radioactive iodine accumulation suspected for brain metastasis.

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