Coexistent thyroid and lung cancers resembling “flip-flop” phenomenon

Daniela Cavaco1 | Davide Fraga2 | Teresa Ferreira2

1Department of Endocrinology, Instituto Português de Oncologia de Lisboa Francisco Gentil, EPE, Lisbon, Portugal
2Department of Nuclear Medicine, Instituto Português de Oncologia de Lisboa Francisco Gentil, EPE, Lisbon, Portugal

Correspondence
Daniela Cavaco, Department of Endocrinology, Instituto Português de Oncologia de Lisboa Francisco Gentil, Street Prof. Lima Basto, Lisboa, Lisbon, 1099-023, Portugal.
Email: daniela.rcavaco@gmail.com

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1 | INTRODUCTION

Differentiated thyroid cancer (DTC) prognosis is usually favorable, even when metastatic radioiodine avid disease is present. For this reason, RAI is considered the gold standard in the treatment of metastatic disease.1 Tumor burden assessment should be based on imaging including high-resolution neck ultrasonography, or CT scanning of neck, chest, abdomen, and sometimes brain, in addition to assessment for bone metastases by scintigraphy and CT1,2 The radioiodine-refractory disease, usually a sign of higher aggressiveness, can be detected by 18F-FDG-PET/CT.2 There is an inverse relationship between iodine and 18F-FDG accumulation in thyroid cancer lesions, the so-called “flip-flop” phenomenon: when thyroid cancer cells dedifferentiate they tend to lose their radioiodine avidity and start taking up 18F-FDG.3,4 In nonDTC (with no 131I avidity), Leboullex et al (2007) found the sensitivity of 18FDG-PET/CT was 83%, influenced by tumor dedifferentiation and tumor burden, and the specificity was 84%.1,5 18FDG-PET scanning may also be considered as part of initial staging in poorly differentiated thyroid cancers, especially those with elevated serum Tg levels but also as a prognostic tool in patients with metastatic disease to identify lesions, patients at highest risk for rapid disease progression, and disease-specific mortality.1,5,6 We present a case of advanced DTC with large tumor burden with heterogeneous uptake of iodine and 8F-FDG.

2 | CLINICAL CASE

A 69-year-old woman with a past history of asthma and right hemithyroidectomy 8 years before (2011), due to a
70-mm hyperplastic nodule, was referred to our center. The patient had a painful lesion in the right acromion. The biopsy suggested papillary thyroid cancer (PTC) metastasis. Histological review of slides of the previous right hemithyroidectomy revealed PTC (encapsulated follicular variant) with lymphovascular invasion. Neck ultrasound from the remaining thyroid showed a spongiform nodule of 8 mm and excluded pathological lymph nodes. However, CT scan documented extensive metastatic disease in the upper mediastinum, lungs (with micronodules and a large lesion with 49 mm in the lower left lobe), chest wall, and right acromion (Figure 1). Thyroidectomy totalization was decided and she was submitted to left hemithyroidectomy. The histology revealed no neoplastic lesions.

The patient was submitted to radiotherapy, 20 Gy, divided in 5 fractions, with improvement of the shoulder pain. Then, she was submitted to therapy with 5.55 GBq of radiiodine-stimulated thyroglobulin was >300,000 ng/mL (NR <25) and whole-body scintigraphy (131I-WBS) after therapy revealed metastatic disease in the right shoulder, left and posterior chest wall, pelvis, and left femur but no uptake in the lungs and mediastinum (Figure 2). 18F-FDG-PET/CT was performed and revealed several lesions with elevated metabolism in the mediastinum, pulmonary left hilum, and lower left lobe with 61 mm (SUVmax 22) and contralateral lung, while the bone lesions referred on 131I-WBS only showed a slight to moderate metabolism (SUVmax up to 7) (Figure 3). Due to the different uptake pattern of the two radiopharmaceuticals by the various lesions, the lung and mediastinic lesions were biopsied by bronchoscopy; the immunohistochemistry was negative for thyroglobulin and paired box gene 8 (PAX 8) and positive for transcription termination factor 1 (TTF1), suggesting lung adenocarcinoma. The patient was referred for a second RAI therapy with 5.55 GBq. This time, the stimulated thyroglobulin was 3106 ng/mL (NR <25). The 131I-WBS (with SPECT/CT) revealed a less intense uptake in the bone lesions. At the moment, the patient has a score 1 in ECOG scale of performance status, presenting with nonproductive cough. She initiated lung-directed treatment with a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (gefitinib 250 mg id).
3 | DISCUSSION/CONCLUSIONS

In this patient, a metastatic disease with a large tumor burden of DTC was admitted due to an elevated thyroglobulin (>300,000ng/ml) and multiple bone and lung lesions documented on CT. At first glance, the absence of evident visualization of the lung and mediastinic lesions on $^{131}$I-WBS after therapy could be attributed to overlapping of structures on a planar image (the use of SPECT or SPECT/CT could have obviated this problem) or it could be due to heterogeneous iodine avidity within the various thyroid-related lesions. In this last scenario, these lesions would correspond to areas of loss of expression of the NIS transporter with lower cell differentiation. $^{18}$FDG-PET/CT confirmed the distinct metabolic patterns, with lung lesions with elevated uptake and bone lesions with lower uptake. This case shows the importance of $^{18}$F-FDG-PET/CT as a complementary evaluation to $^{131}$I-WBS, in the presence of detectable $^{131}$I uptake in metastasis with significant tumor burden. $^{18}$F-FDG uptake may be present in malignant lesions with no $^{131}$I uptake or slight uptake. Poorly differentiated thyroid cancer is a burdensome illness with poor prognosis compared with other thyroid cancers, although the careful choice and interpretation of complementary imaging tools allowed the differential diagnosis of two distinct malignant entities, with a serious impact on the final prognosis of the patient. In conclusion, in the presence of “flip-flop” phenomenon, a well-described characteristic of progressive DTC, a high suspicion index must be maintained when the findings are discordant, in order to provide an appropriate differential diagnosis and management of the disease.

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AUTHOR CONTRIBUTIONS
The authors declare that all authors had a substantial contribution for this manuscript. The authors declare that all authors approve the final version of the manuscript. The authors declare that the manuscript has not been previously presented.

ETHICAL APPROVAL
The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association. The authors declare that the manuscript, complete or in parts, does not infringe any copyright and does not violate any privacy rights. The authors declare that no experiments were performed on humans or animals for this investigation. The authors state that subject has given his written consent.

FIGURE 3 First row (A, B, and C): $^{131}$I SPECT/CT performed after the second therapy shows no uptake in the pulmonary lower left lobe lesion (yellow arrows). Second row (D, E, and F): $^{18}$F-FDG-PET/CT shows high FDG uptake on the lower left lobe lesion (green arrows) with SUVmax 22.7. D – MIP; E – Axial section; F – Sagittal section.
informed consent to publish his case, including publication of images.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID
Daniela Cavaco https://orcid.org/0000-0001-9486-9791

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