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Differential tumor biology between locoregional and distant metastasis in a patient with TENIS with TKI-resistant aggressive recurrent disease: a comparative evaluation with FDG, ^{68}Ga-DOTATATE and ^{68}Ga-PSMA-11 PET-CT

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Key Words: Thyroid Carcinoma; TENIS; FDG; ^{68}Ga-DOTATATE; ^{68}Ga-PSMA-11; PET-CT

Abstract:

The molecular PET-CT imaging profile of an interesting case of differentiated thyroid carcinoma, later transformed into with thyroglobulin elevation and negative iodine scintigraphy (TENIS) with tyrosine kinase inhibitor (TKI) resistant recurrent aggressive disease, is presented. The patient was evaluated to assess SSTR-2 or PSMA expression to explore the possibility of any effective targeted nuclear therapy. ^{18}F-FDG, ^{68}Ga-DOTATATE and ^{68}Ga-PSMA-11 PET/CT was performed, which revealed tracer avidity in all 3 scans in the extensive loco-regional disease of large ill-defined retropharyngeal and retro-tracheal soft tissue eroding cricoid cartilage, extending into tracheal lumen and left sided strap muscles. On the contrary, there was no definite uptake in the multiple bilateral lung nodules, the scan findings indicating a differential tumor biology between loco-regional and distant metastasis.

Introduction:

TENIS is the major cause of mortality and morbidity in patients of differentiated thyroid carcinoma (DTC) as no definitive/effective targeted nuclear therapy is available. In approximately 20-30% of patients with metastatic/ recurrent DTC, there is evidence of lack of sodium iodide symporter (NIS) expression, having negative radioiodine scintigraphy and thus, refractory to radioiodine treatment. Preliminary reports show that such tumors may express somatostatin receptors SSTR-2 on their cell surface or there can be prostate-specific membrane antigen (PSMA) overexpression secondary to tumor neovasculature, the latter is expressed by the tumor vascular endothelium in a variety of cancers [1]. PSMA expression in TENIS for potential treatment options is confirmed by recent studies in differentiated thyroid cancer [2,3,4]. Thus, non-invasive imaging for SSTR-2/PSMA expression in TENIS is being explored for potential definitive/ effective treatment options in differentiated thyroid cancer.

Case Report

An 85-year-old male, diagnosed with papillary thyroid cancer with no extrathyroidal or nodal involvement underwent total thyroidectomy, after two years had re-surgery for locoregional recurrence. Patient had relapsed locoregional disease after another 3 years with inoperable disease, for which he was treated with multiple oral radioiodine therapies (cumulative dose: 620 mCi or 22.94 GBq). On subsequent follow-up, he had negative diagnostic ^{131}I whole-body scan with persistent disease, elevated thyroglobulin, thus, underwent external radiotherapy for locoregional disease control. Despite on thyroxin suppression, there was persistent rising thyroglobulin levels, ^{18}F-FDG-PET/CT showed ill-defined hypermetabolic mass in the tracheo-oesophageal groove, abutting the trachea anteriorly and the oesophagus posteriorly and reaching up to the paravertebral region at D1/D2 level. Ametabolic multiple tiny bilateral lung nodules (largest 1.3cm) were observed. The patient was started on TKI (sorafenib and later on, lenvatinib) and monitored by FDG-PET/CT. On TKI, the patient developed difficulty in swallowing and rising serum thyroglobulin levels of 351.27 ng/ml, despite adequately suppressed thyroid-stimulating hormone with negative antithyroglobulin antibodies.

This patient with lack of NIS expression was re-evaluated to assess any expression of somatostatin receptors or PSMA to examine the possibility of any effective targeted nuclear therapy, by ^{18}F-FDG, ^{68}Ga-DOTATATE (assessing primarily *SSTR2* expression levels in the tumor cells) and

^{68}Ga-PSMA-11 (reflecting expression of a type II membrane protein PSMA in tumor neovasculature endothelial cells) PET/CT (Fig 1 and 2) after approval by institutional ethics committee. All 3 scans whole body PET/CT were compared. There was a locoregional ill-defined retropharyngeal and retro-tracheal soft tissue measuring 5.0 x 3.7x 3.5 cm in size eroding cricoid cartilage, anteriorly extending into tracheal lumen, posteriorly abutting prevertebral fascia, laterally on left side involving strap muscles and abutting the common carotid artery. Quantitative uptake of each tracer revealed ^{18}F-FDG SUVmax 5.8, ^{68}Ga-DOTATATE SUVmax 18.3 and Krenning score 3 (liver 14.4 & spleen 36.6), ^{68}Ga-PSMA-11 SUVmax 19.5 and miPSMA score 3 (parotid:18.3). There were distant multiple bilateral lung nodules, the largest measuring 1.3 x 1.1 cm in right middle lobe, rest all smaller with no definite uptake in any of the three PET-CT studies (Fig 1 and 2). The patient was considered for palliative ^{177}Lu-PSMA-617 therapy, the post-therapy scan showed adequate uptake in the upper mediastinal soft tissue and will follow up after 2 months. Locoregional pain and ease in swallowing indirectly improved quality of life within one month post- therapy. This case demonstrated differential tumor biology between tracer positive extensive locoregional disease (FDG, ^{68}Ga-PSMA-11 and ^{68}Ga-DOTATATE with high miPSMA and Krenning scores) and tracer negative distant lung metastases in the same individual.

Discussion:

Silberstein in his recent publication stated physicians caring for patients with the TENIS syndrome are urged to enter them in clinical therapeutic studies whenever possible [5]. The TENIS tumors show variable expression of somatostatin receptors- SSTR-2 on their cell surface [6,7,8] or PSMA in tumor neovasculature on the apical surface of endothelial cells [9]. ^{68}Ga-DOTATOC/TATE- PET/CT can be used for visualization of SSTR-2 expressing lesions. However, not all patients with TENIS lesions express SSTR-2[6,7,8]. PSMA expression in TENIS for potential treatment options is confirmed by recent studies in differentiated thyroid cancer [10,11,12]. PSMA representing marker of neovasculature formation expressed by DTC, has been proposed to contribute in the prediction of tumor aggressiveness and patient outcome [13]. One of the reasons for lack of uptake in the lung metastases by all 3 tracers could also be secondary to limitation of PET spatial resolution and partial volume effect, particularly considering the small size of most lesions (largest nodule size 1.3 cm). In TENIS, the visual evaluation by Krenning's (^{68}Ga-DOTATATE) and miPSMA (^{68}Ga-PSMA-11) scoring systems is a promising approach in exploring the tumor biology in metastatic disease and can create possibility of targeted therapy with^{177}Lu-DOTATATE/ PSMA therapy, depending on the tracer avidity on^{68}Ga-DOTATATE/ ^{68}Ga-PSMA-11 PET-CT [14]. A high uptake (such as in this case, the miPSMA score 3 & Krennings score 3 uptake in the aggressive loco-regional disease) potentially qualifies for targeted SSTR/ PSMA based therapies as promising alternatives, in the absence of other treatments.

In conclusion, the present case highlighted the differential tumor biology between positive extensive loco-regional disease and negative distant lung metastasis, explored by the molecular imaging with PET-CT.

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Figure 1

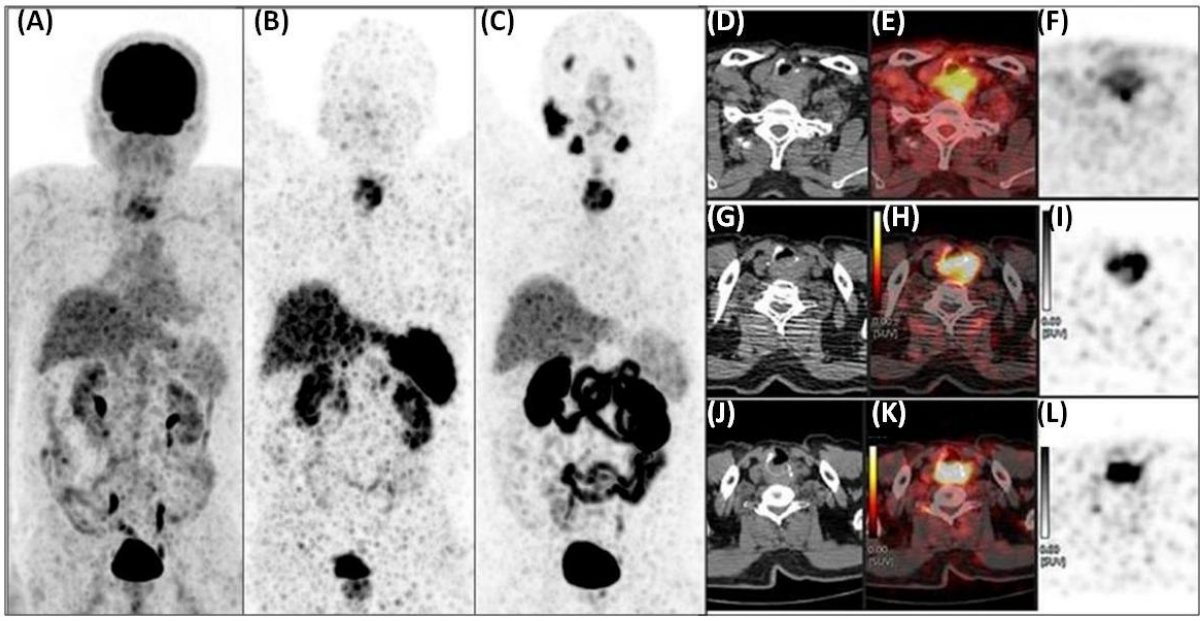

Figure 1: Maximum intensity projection anterior PET images (**A)** ^{18}F-FDG PET**, (B)** ^{68}Ga-DOTATATE**, (C)** ^{68}Ga-PSMA-11; **(D,E,F)** CT, fused FDG PET/CT and 18F-FDG PET transaxial images; (**G,H,I)** CT, fused 68Ga-DOTATATE PET/CT and 68Ga-DOTATATE PET axial images; **(J,K,L)** CT, fused 68Ga-PSMA and PET/CT 68Ga-PSMA PET axial images; showing soft tissue in retropharyngeal space with tracheal invasion and posteriorly abutting prevertebral fascia with SUVmax values: ^{18}F-FDG 5.8; ^{68}Ga-PSMA-11 19.5, miPSMA score 3; ^{68}Ga-DOTATATE 18.3, Krennings score 3.

Figure 2

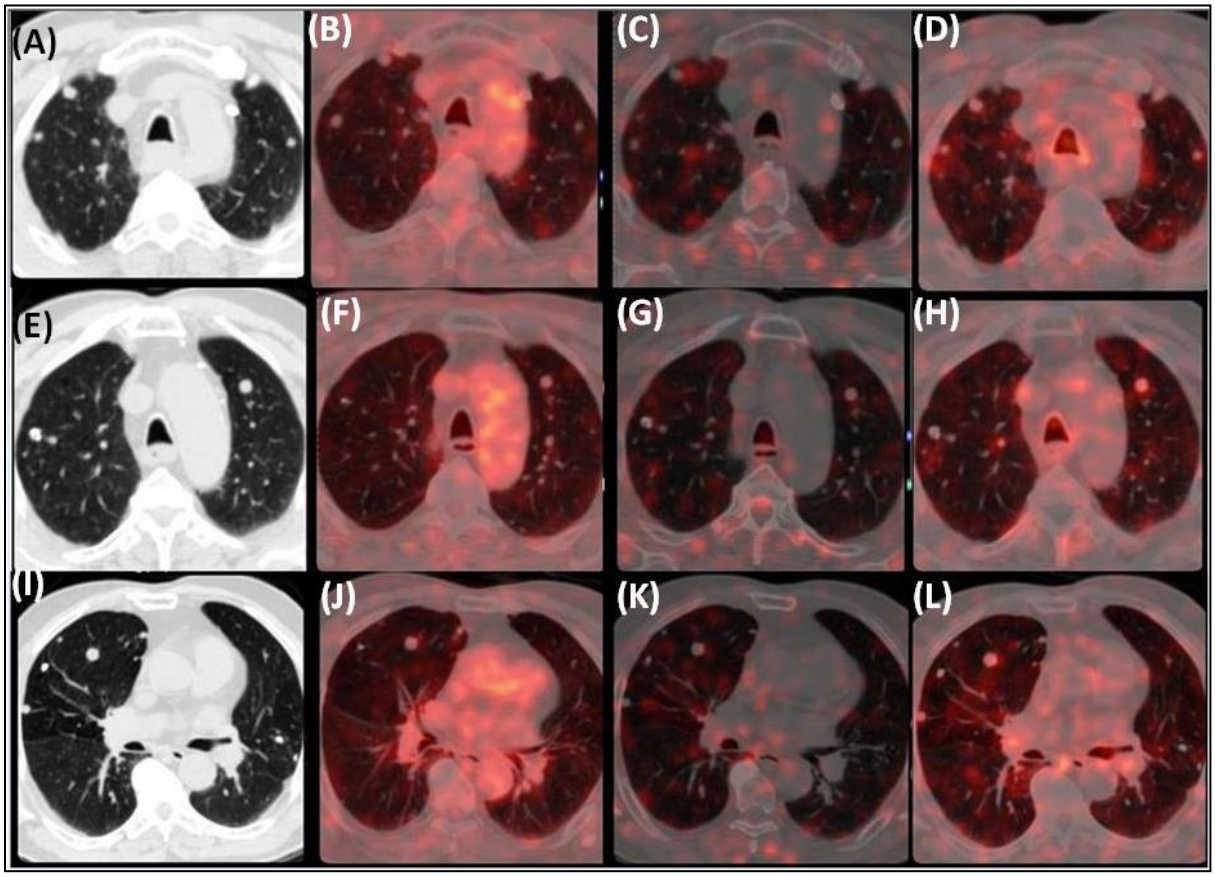

Figure 2: **(A,E,I)** CT (lung window) transaxial images; **(B,F,J)** ^{18}F-FDG-PET/CT (lung window) fused transaxial images**; (C,G,K)** ^{68}Ga-DOTATATE (lung window) fused transaxial PET/CT; **(D,H,L)** ^{68}Ga-PSMA PET/CT (lung window) fused transaxial images, show non-tracer avid multiple bilateral lung nodules.