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Dual Tracer ^{18}F-Fluorocholine and ^{18}F-DCFPyL PET/CT in the Assessment of a Small Cell Neuroendocrine Transformation of Metastatic Prostate Cancer

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Abstract

The small cell neuroendocrine variant is a rare subset of prostate cancer. We present the case of a patient who underwent a dual tracer ^{18}F-Fluorocholine and ^{18}F-DCFPyL PET/CT in the context of biochemical recurrence. Completely discordant results were found using both radiotracers, defining the biological heterogeneity in tumor expression and treatment response.

Keywords: ^{18}F-Fluorocholine; ^{18}F-DCFPyL; PET/CT; Small cell neuroendocrine prostate cancer; Dual tracer

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Introduction

The Small Cell Neuroendocrine Prostate Cancer (SCNPC) is a complex androgen-independent phenotype that may arise *de novo* (between 0.5% and 2%), although its prevalence increases in later stages of prostate cancer progression (up to 20%), especially in the setting of hormone-refractory disease, probably coexisting differentiated luminal secretory phenotype with neuroendocrine features [1]. The biologic heterogeneity of metastatic SCNPC has been scarcely previously defined using different PET radiotracers demonstrating discordant uptake pattern [2,3].

Case Presentation

We present the case of a 71-year-old man in his first biochemical recurrence with a Prostate Specific Antigen (PSA) of 0.7 ng/mL and a duplication time of 4.7 months. Patient was diagnosed of a high-risk prostate cancer treated with prostatectomy plus lymphadenectomy three years ago (Gleason 9, pT3bN0). No Androgenic Deprivation Therapy (ADT) was administered.

Patient underwent a double radiotracer PET/CT with ^{18}F-Fluorocholine and ^{18}F-DCFPyL, [2-(3-(1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl)-ureido)-pentanedioic acid], a second generation high affinity ligand against Specific Prostate Membrane Antigen (PSMA), following the instructions of the ongoing PYTHON prospective clinical trial (EudraCT number 2020-000121-37), whose primary objective is to compare the detection rate of ^{18}F-DCFPyL PET/CT *vs.* that of ^{18}F-Fluorocholine PET/CT, in the setting of the first biochemical recurrence of patients who underwent definitive therapy (prostatectomy, external beam radiotherapy or brachytherapy).

^{18}F-Fluorocholine PET/CT showed a moderate hypermetabolism of a pelvic mass with non-avidity for ^{18}F-DCFPyL (Figure 1, 2). On the other hand, isolated bone metastases were revealed only in the ^{18}F-DCFPyL PET/CT.

After 4 cycles of chemotherapy (carboplatin plus etoposide) a faint increase of PSA (1.1 ng/mL, February 2021) was detected. Post-chemotherapy ^{18}F-DCFPyL revealed bone progression with partial response of pelvic mass on ^{18}F-Fluorocholine PET/CT (Figure 2, 3). ADT was initiated, decreasing PSA to undetectable values in the follow-up.

Discussion

Although the majority of prostate cancer cells possessing luminal (secretory) phenotype and a minor cell population demonstrating neuroendocrine features (no more than 1% of the entire tumor

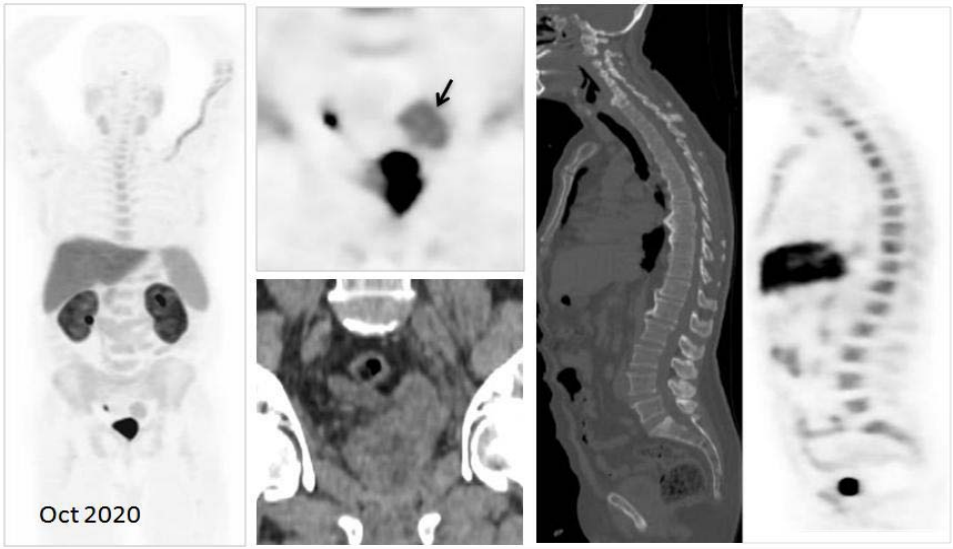

Figure 1: Moderate hypermetabolism in a left pelvic mass, closed to superior border of bladder on ^{18}F-Fluorocholine PET/CT (arrow). A diffuse mild bone marrow uptake, without focal deposits, probably of physiologic origin, is observed.

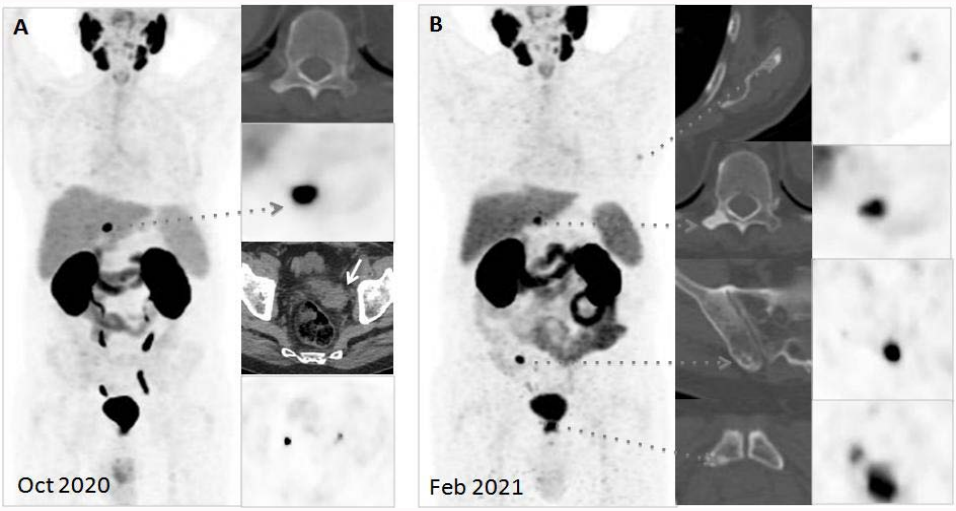

Figure 2: Baseline 2-(3-{1-carboxy-5-[(6-[^{18}F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid (^{18}F-DCFPyL) PET/CT (A) showed intense uptake in a lytic bone metastases (right transverse apophysis of D11). No ^{18}F-DCFPyL uptake was observed on pelvic mass (arrow). Bone progression on post-chemotherapy ^{18}F-DCFPyL with three new lesions on left scapula; right iliac and right pubic bone (B).

cell population), a significant portion of advanced and recurrent tumors, especially in castration resistance, has pure neuroendocrine phenotype known as SCNPC. However, the transformation of adenocarcinoma into SCNPC is not well explained based on it can develop from luminal type tumor cells (Trans differentiation) or from the neuroendocrine tumor cells (clonal expansion) [4].

Progressive SCNPC is characterized by the presence of visceral metastases, with high proportion of lytic bone disease [5]. Because tumor cells of SCNPC do not express PSA, patients often show low serum PSA levels relative to their tumor burdens.

Since SCNPC cells are independent to Androgen Receptor (AR) function, not expressing AR, and do not respond to AR-targeted therapy, chemotherapy is an option, but with usually limited benefits, as in the present case [6-8].

The biologic heterogeneity of metastatic SCNPC has been scarcely previously defined using different PET radiotracers demonstrating discordant and contradictory uptake pattern. In histologically confirmed SCNPC lesions high ^{18}F-FDG uptake has been reported and, on the contrary, no significant uptake using ^{18}F-Fluorocholine or ^{68}Ga-PSMA [9,10].

Others have described high ^{68}Ga-PSMA and ^{68}Ga-DOTATOC avidity in a probable neuroendocrine tumor differentiation within the primary prostate cancer but negative with ^{18}F-FDG [11].

Affinity of ^{18}F-DCFPy by PSMA is five times higher compared to the first generation radiotracers as ^{18}F-DCFBC, N-[N-[(S)-1,3-dicarboxypropyl]carbamoyl]-4-(18)F-fluorobenzyl-L-cysteine, with Standardized Uptake Values (SUV) similar to other PSMA PET ligands [12].

There have not been reported differences between ^{18}F-DCFPyL with other PSMA ligands regarding detection rates on biochemical

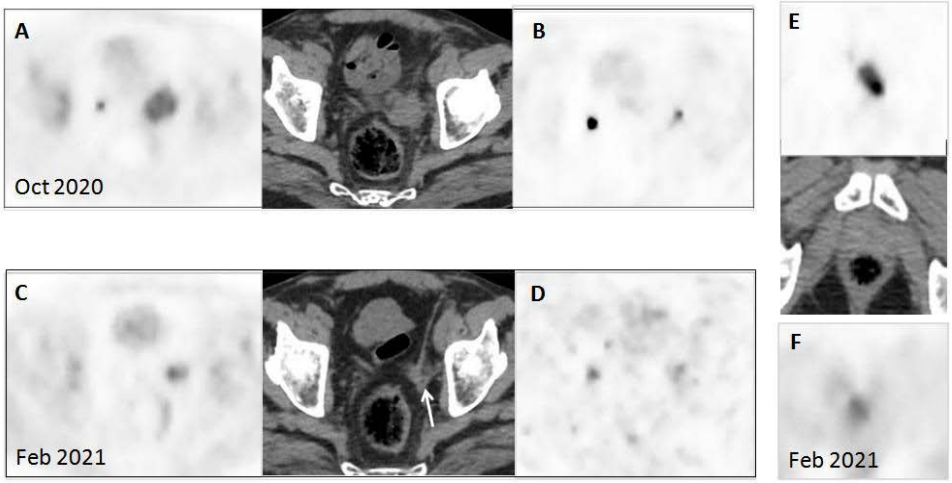

Figure 3: Pelvis mass on baseline ^{18}F-Fluorocholine (A) and ^{18}F-DCFPyL (B) PET/CT (arrow). Reduction in lesion size and metabolism on ^{18}F-Fluorocholine (C) with a negative ^{18}F-DCFPyL PET/CT (D). Moreover a more intense peri-urethral prostate bed uptake was defined with ^{18}F-DCFPyL PET/CT (E) compared to ^{18}F-Fluorocholine (F) suspicious of local progression.

recurrence [13]. In addition, although increased prostate cancer grade, progression and castrate resistance is associated to higher cell-membrane PSMA expression, PSMA-targeted imaging would be unable to reliably identify neuroendocrine prostate cancer [14,15].

By our knowledge, this is the first reported experience of the use of ^{18}F-DCFPyL joined to ^{18}F-Fluorocholine PET/CT in the metastatic SCNPC detection, illustrating the heterogeneous molecular aspects of the disease.

In summary, dual-tracer ^{18}F-DCFPyL and ^{18}F-Fluorocholine PET/CT seems to have a potential utility in theranostics in metastatic prostate cancer with evidence of SCNPC transformation, guiding treatment decision making and in monitoring the response to multimodality therapy.

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