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ORIGINAL PAPER

Ductal prostate cancer staging: Role of PSMA PET/CT

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Summary ***Introduction: To evaluate the accuracy of PSMA PET/CT in the diagnosis and clinical staging of prostatic ductal adenocarcinoma (DAC).***
Materials and methods: Two Caucasian men 58 and 62 years old were admitted to our Department for dysuria: the patients had not familiarity for prostate cancer (PCa), PSA values were 5.6 and 2.8 ng/ml, digital rectal examination was positive, multiparametric magnetic resonance image (mpMRI) showed for both the presence of an index lesion PIRADS score 5. The patients underwent extended transperineal prostate biopsy combined with four mpMRI/TRUS fusion biopsy under sedation and antibiotic prophylaxis; biopsy histology demonstrated the presence of a mixed PCa characterized by DAC and acinar PCa (Grade Group 4/Gleason score 8). The patients underwent clinical staging performing lung and abdominal CT, bone scan and fluoride 18 (18F) PSMA PET/CT.
Results: Conventional imaging was negative for distant metastases; 18F-PSMA PET/CT showed in both patients an intraprostatic lesion characterized by a standardized uptake value (SUVmax) equal to 4.6 and 4.9 in the absence of distant lesions suspicious for metastases. Following multidisciplinary evaluation, the patients underwent radical prostatectomy plus extended pelvic lymphadenectomy. Definitive specimen showed the presence in both cases of a mixed pT3bN1 PCa (ductal plus acinar pattern Grade Group 4) with positive surgical margins, neuronal invasion, and nodes metastases (5/20 and 6/24, respectively). Post-operative PSA in the two patients was 0.8 and 0.3 ng/ml, therefore patients underwent adjuvant therapy.
Conclusions: Conventional imaging and PSMA PET/CT could result inadequate in clinical staging of DAC, the use of more imaging data (i.e. mpMRI and/or F-18 FDG) could improve overall accuracy.

KEY WORDS: PSMA PET/CT; Prostate cancer; Ductal PCa; Ductal PCa staging.

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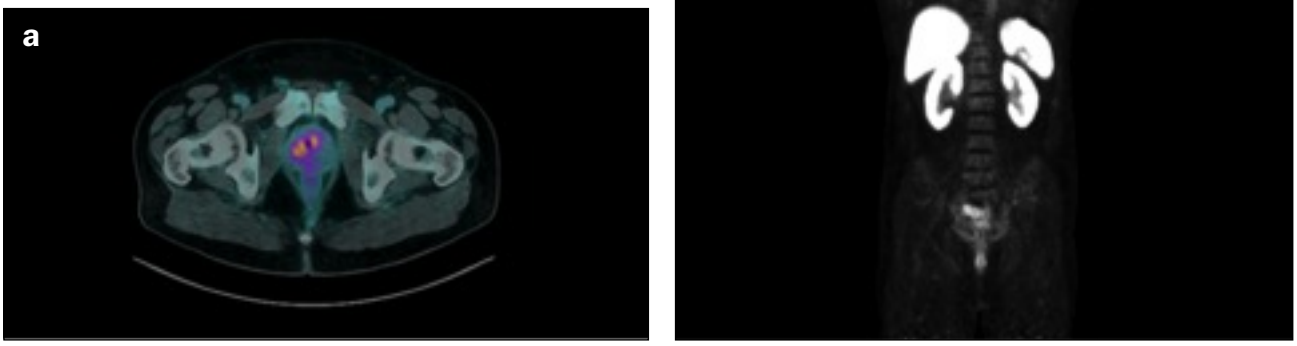
INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed malignancy in men; although, conventional imaging with *computed tomography* (CT) and technetium-based bone scan are widely used for staging, recently, cumulative evidence indicates that *prostate-specific membrane antigen* (PSMA) *positron-emission tomography* (PET/CT) should be a centerpiece of diagnosis and staging for intermediate/high risk patients (1-5). Although, PSMA PET/CT seems about 27% more accurate than conventional imaging (6), 5-10% of primary PCa tumours have low PSMA activity which evade detection by PSMA PET, mostly in high-grade and variant tumour types (7-10).
Prostatic *ductal adenocarcinoma* (DAC) is an uncommon variant of prostatic carcinoma with aggressive behavior and worse prognosis and, still today, the of role PSMA PET/CT in its diagnosis and staging has not been clearly established (11).
We evaluated the accuracy of fluoride 18 (18-F) PSMA PET/CT in the diagnosis and clinical staging in two patients with DAC.

CASE REPORT

Two Caucasian men 58 and 62 years old were admitted to our Department for dysuria: the patients had not familiarity for PCa and assumed antihypertensive drugs. PSA values were equal to 5.6 and 2.8 ng/ml, digital rectal examination was highly suspicious for PCa and magnetic resonance image (mpMRI) showed for both the presence of a index lesion *Prostate Imaging Reporting and Data System* (PIRADS) score 5. The patients underwent extended transperineal prostate biopsy (18 cores) combined with four mpMRI/TRUS fusion biopsy using a 18 gauge needle under sedation and antibiotic prophylaxis (12, 13). The biopsy histology demonstrated the presence of a mixed PCa characterized by ductal and acinar PCa (Grade Group 4/Gleason score 8) with a Greatest Percentage of Cancer equal to 100%, a mean number of positive cores of 15 (3 targeted cores and 12 systematic biopsies)) and a mean total percentage of cancer equal to 45% (35-55%).
The clinical staging performing lung and abdominal CT plus technetium-based bone scan did not demonstrate distant metastases and/or others primitive tumors; in addition, the 18-F PSMA PET/CT (5) showed in both patients an intraprostatic lesion provided of a standardized uptake value (SUVmax) equal to 4.6 and 4.9 in the absence of distant lesions suspicious for metastases (Figure 1). Following multidisciplinary evaluation, the patients underwent open *radical prostatectomy* (RP) plus extended pelvic lymphadenectomy. Definitive specimen showed the presence in both cases of a mixed pT3bN1 PCa (ductal plus acinar Grade Group 4/Gleason score 8) with positive surgical margins, perineuronal invasion and nodes metastases (5/20 and 6/24, respectively). Post-operative PSA (one month from surgery) in the two patients was 0.8 and 0.3 ng/ml, therefore patients under-

Figure 1.
18-F PSMA PET/CT in man with mixed prostate cancer (ductal plus acinar PCa Grade Group 4/Gleason score 8): intraprostatic standardized uptake value (SUVmax) was equal to 4.9 (a) in the absence of distant metastases (b).



went adjuvant radiotherapy of prostatic fossa and *androgen deprivation therapy* (ADT).

Discussion

DAC is rare, aggressive, and characterized by cancer involving ducts and/or acini usually associated with a high-grade Gleason score/Grade Group, large tumor volume, and adverse prognostic parameters, including extraprostatic extension and seminal vesicle invasion (14, 15). In the WHO Classification fifth edition the term 'ductal adenocarcinoma' is now reserved for those radical prostatectomy cases with more than 50% ductal morphology, while in needle biopsy cases the term 'adenocarcinoma with ductal features' is recommended for both pure ductal and mixed ductal and acinar features (16). Although DAC is treated with conventional therapies, it demonstrated worse outcomes in comparison with high-grade acinar PCa, regardless of the treatment modality. *Ranasinghe et al.* (17) in 228 men with DAC submitted to RP *vs.* radiotherapy demonstrated a 5-yrs *overall survival* (OS) and *metastases free survival* (MFS) equal to 75 *vs.* 62% and 88 *vs.* 82%, respectively; in addition, 76 men who received adjuvant/salvage ADT after RP, DAC also had worse MFS and OS and was characterized in 91% of them by intrinsic upregulation of androgen-resistant pathways. Although mpMRI and PSMA PET/CT are provided of superimposable accuracy in the diagnosis of high risk PCa (12, 18) showing direct correlation between PIRADS score and SUVmax values (19), in the presence of DAC only mpMRI (20) allows to perform diagnosis because PSMA PET/CT demonstrated a very limited diagnostic accuracy (21). In this respect, PSMA uptake has sometimes been poor compared with prominent 18-flourodeoxyglucose (F-18 FDG) avidity, which would suggest that FDG PET/CT scans are important in staging of ductal pattern (22, 23). The diagnostic utility of dual-tracer FDG/PSMA PET/CT for PCa may assist in characterizing high-risk disease during primary staging and restaging especially with concurrently negative PSMA PET. When applied to high-risk or variant histology (i.e., DAC), detection of the FDG-positive phenotype may signal a poorer prognosis to prompt more aggressive intervention earlier in the disease course and dual PSMA/FDG PET/CT may improve oncological outcomes (24); in definitive, the use of PSMA and FDG PET imaging in PCa should be examined individually and the potential diagnostic impact for individual patients to undergo dual-tracer PET imaging could be reserved in case of inconclusive conventional imaging and/or negative PSMA PET (25).

In our series, both the patients had a negative conventional imaging (CT and technetium-based bone scan) and 18F PSMA PET/CT despite a locally advanced disease with the presence of metastatic nodes (pT3bN1) underlining the lower accuracy of imaging in local and distant staging in case of DAC.

In conclusion, conventional imaging and PSMA PET/CT could result inadequate in clinical staging of DAC, the use of more imaging data including mpMRI and F-18 FDG could improve overall accuracy.

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