Uptake of [^{18}F]DCFPyL in Paget's Disease of Bone, an Important Potential Pitfall in the Clinical Interpretation of PSMA PET Studies

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Abbreviations: 2-(3-{1-Carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ([^{18}F]DCFPyL), bone scan (BS), computed tomography (CT), contrast-enhanced computed tomography (CECT), magnetic resonance imaging (MRI), methylene diphosphonate (MDP), positron emission tomography (PET), prostrate cancer (PCa), prostate-specific membrane antigen (PSMA), standardized uptake value (SUV)

ABSTRACT

Prostate-specific membrane antigen (PSMA)-targeted positron emission tomography (PET) imaging is an emerging technique for evaluating patients with prostate cancer (PCa) in a variety of clinical contexts. As with any new imaging modality, there are interpretive pitfalls that are beginning to be recognized. In this report, we describe the findings in a 63-year-old male with biochemically recurrent PCa after radical prostatectomy who was imaged with 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ([^{18}F]DCFPyL), a small-molecule inhibitor of PSMA. Diffuse radiotracer uptake was noted throughout the sacrum, corresponding to imaging findings on contrast-enhanced computed tomography (CT), bone scan, and pelvic magnetic resonance imaging consistent with Paget's disease of bone. The uptake of [^{18}F]DCFPyL in Paget's disease most likely results from hyperemia and increased radiotracer delivery. In light of the overlap in patients affected by PCa and Paget's disease, it is important for nuclear medicine physicians and radiologists to be aware of the potential for this diagnostic pitfall when interpreting PSMA PET/CT scans. Correlating findings on conventional imaging such as diagnostic CT and bone scan can help confirm the diagnosis.

INTRODUCTION

Limitations in conventional imaging for evaluating prostate cancer (PCa) have spurred the development of several new positron emission tomography (PET) molecular imaging agents. Among the most extensively studied radiotracers are small-molecule inhibitors of prostate-specific membrane antigen (PSMA) (1-3), a transmembrane enzyme that is highly expressed in PCa and the expression of which is positively correlated with aggressive features of the disease (4-6).

These small-molecule imaging agents have demonstrated several important findings in early clinical studies of PCa patients, including (1) the reliable identification of clinically significant disease in preprostatectomy patients (7), (2) greater sensitivity for identifying sites of disease in patients with metastatic PCa compared with conventional imaging with contrast-enhanced computed tomography (CECT) and [^{99m}Tc]methylene diphosphonate (MDP) bone scan (BS) (8), and (3) higher sensitivity than conventional imaging for detecting lesions in patients with biochemical recurrence after prostatectomy (9). The specificity of these agents is also quite high and has been reported to be up to 100% in some series with pathological correlation (10). Despite this high apparent specificity, potential false positives have been noted in the literature, including radiotracer uptake in celiac ganglia (11) and an adrenal adenoma (12).

In this report we describe the uptake of the PSMA-targeted radiotracer 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ([^{18}F]DCFPyL) (3) in Paget's disease of bone, a common condition in the same elderly male population that is at risk for PCa. Particularly in light of the propensity for PCa to metastasize to bone, potential false-positive bone lesions could significantly confound the interpretation of PSMA PET scans.

METHODS

The patient is a 63-year-old man who underwent a radical retropubic prostatectomy approximately 4 years before the imaging discussed herein. Final surgical pathology demonstrated

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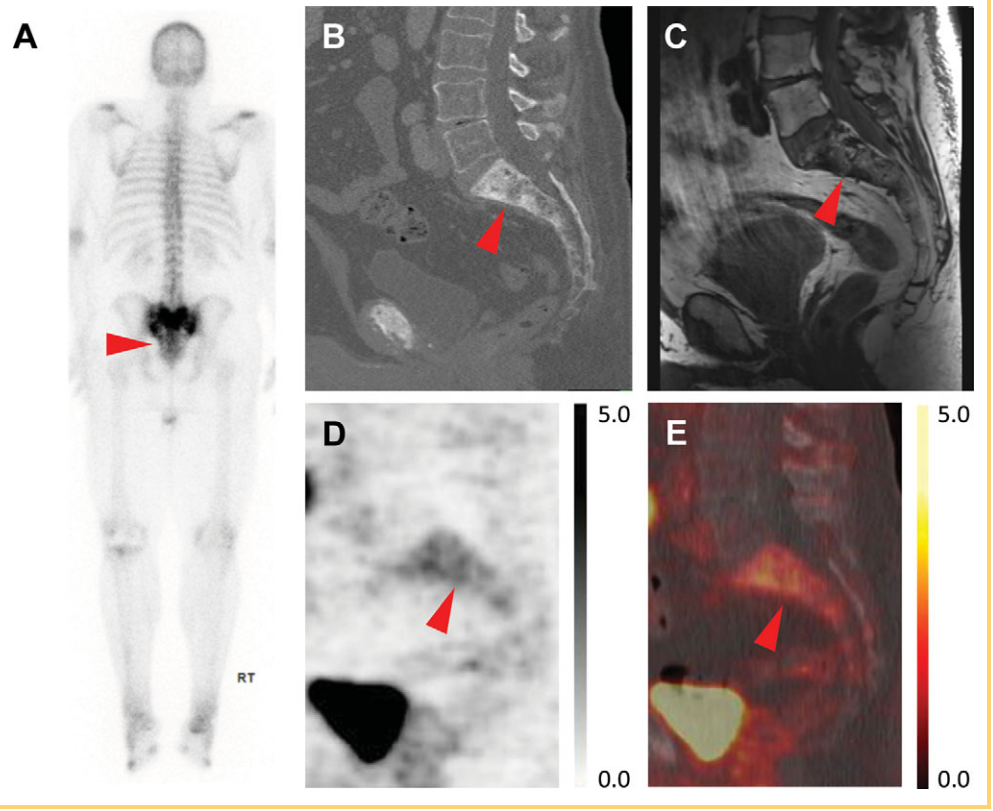

Figure 1. (A) Posterior projection whole-body MDP BS, (B) sagittal CECT image through the sacrum, (C) sagittal T1-weighted noncontrast, nonfat-saturation MRI, (D) sagittal [18F]DCFPyL PET image through the sacrum, and (E) sagittal [18F]DCFPyL PET/CT-fused image through the sacrum demonstrating patient's sacral Paget's disease. Note the thickened trabecular pattern on CECT corresponding to intense MDP uptake, normal high T1 signal upon MRI, and diffuse mild [18F]DCFPyL uptake.

Gleason score 4 + 3 = 7, pT3bN1 PCa. After surgery, the patient's prostate-specific antigen level became undetectable. Within 1 year, it began to rise to its most recent value of 0.3 ng/mL. Alkaline phosphatase level at the time of imaging was mildly elevated to 158 IU/L (normal laboratory range, 39–117 IU/L).

As part of routine clinical evaluation for biochemically recurrent PCa, the patient underwent imaging with [99mTc]MDP BS. This demonstrated intense radiotracer uptake throughout the sacrum (Figure 1A). In addition, the patient was imaged with a single venous-phase CECT of the abdomen and pelvis that revealed sclerosis of the sacrum with thickening of the trabeculae (Figure 1B). Both of these findings are most compatible with Paget's disease of bone. The CECT and BS were otherwise unremarkable from an oncological perspective. To further evaluate the patient, magnetic resonance imaging (MRI) of the pelvis was performed. The MRI demonstrated irregular sclerosis and trabecular thickening within the sacrum with a preserved high T1 signal compatible with fatty marrow (Figure 1C), further confirming the benign nature of the sacral lesion. Notably, local recurrence within the prostate bed was not seen on the MRI. These findings were clinically deemed consistent with Paget's disease of the sacrum, with no definitive findings on conventional imaging to localize the site of patient's recurrent disease.

Based upon the patient's clinical scenario and imaging findings, he qualified for an institutional review board-approved prospective trial at our institution aimed at evaluating the use of [18F]DCFPyL PET/CT in the context of biochemically recurrent PCa. [18F]DCFPyL was utilized under the auspices of a US Food and Drug Administration Exploratory Investigational New Drug application. Informed consent was obtained from the patient before proceeding with the study PET/CT. Briefly, the PET was acquired 1 hour after the injection of approximately 333 MBq (9 mCi) of [18F]DCFPyL, with the acquisition field of view extending from the midthighs through the skull vertex. A low-dose, noncontrast CT for attenuation correction and anatomic localization was also obtained. Details regarding the acquisition protocol have been previously published (3, 13). Standardized uptake values (SUVs) were determined based on lean body mass.

The [18F]DCFPyL PET/CT was notable for 2 important reasons. First, a focus of intense radiotracer uptake was observed within the prostate bed that was consistent with a local recurrence of the patient's PCa (maximum SUV, 9.3). Second, mild to moderate uptake was seen throughout the sacrum (maximum SUV, 4.6; Figure 1D–E), corresponding to the abnormality at this site seen on the other modalities. Figure 2 demonstrates the MRI-occult (A), [18F]DCFPyL-avid presumed local PCa recurrence (B).

DISCUSSION

Given the immense volume of data that has been generated on the use of PSMA-targeted radiotracers for PCa PET imaging, it is almost certain that this modality will continue to be used extensively in imaging trials and may become a part of the clinical imaging workup of patients with PCa. As more patients are imaged with these radiotracers, it will become increasingly important for radiologists and nuclear medicine physicians to be aware of limitations that might affect their interpretations of these imaging studies. To this end, we have reported mild to moderate [18F]DCFPyL uptake within the sacrum in a patient with conventional imaging findings compatible with Paget's

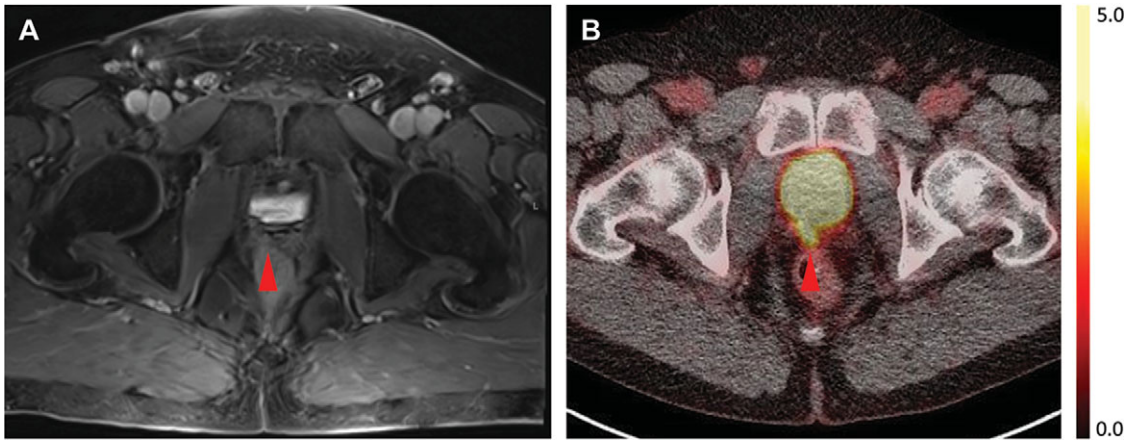

Figure 2. (A) Axial T1-weighted postcontrast MRI and (B) axial [18F]DCFPyL PET/CT images through the prostate bed demonstrating the patient's presumed local recurrence as intense radiotracer uptake on PET/CT but with no corresponding abnormality on MRI. The relative radiotracer uptake in the prostate bed lesion is visually and quantitatively higher than the uptake in the sacrum shown in Figure 1D–E.

disease of the sacrum. This level of uptake will generally be distinguishable from sites of PCa which demonstrate intense uptake (compare Figures 1 and 2); however, in our group's experience, densely sclerotic bone metastatic PCa lesions that are composed predominantly of osteoblastic reactions may contain few viable tumor cells and can also have relatively low PSMA-targeted radiotracer uptake (8). Ultimately, determining true and false-positive findings from PSMA scans will be best ascertained by well-designed prospective trials that incorporate large numbers of patients.

Although Paget's disease is a common benign bone condition in the elderly, affecting up to 10% of the population aged >85 years, its confinement to the sacrum is a somewhat unusual manifestation (14). Elevated serum alkaline phosphate levels can be seen in Paget's disease, as in the patient evaluated in this study; however, osteoblastic metastases from PCa can also present with this laboratory abnormality and should therefore be interpreted with caution (15). Paget's disease can be profoundly hyperemic (to the extent of rarely causing high-output heart failure [16]), and it is this feature that likely leads to mildly increased radiotracer distribution within a Paget's lesion.

Interestingly, a single other case report of Paget's disease of bone imaged with a ^{68}Ga-labeled PSMA-targeted radiotracer was recently published (17). The authors of this report postulated that the high level of uptake could suggest that the target of the radiotracer may be present within the neovasculature of areas of Padget's disease. An alternative hypothesis is that radiotracer accumulation is driven by hyperemia and increased radiotracer delivery. If the latter mechanism is accurate, then it is possible that other underlying etiologies that cause hyperemia (eg, healing bone after trauma or inflammatory processes) may also cause false-positive uptake upon PSMA PET scans.

In this report, the appearance of the sacrum on conventional imaging (Figure 1) was compatible with Paget's disease and did not suggest PCa bone metastasis. The thickened trabeculae on CECT combined with diffusely increased MDP uptake on BS and the lack of fatty marrow replacement indicated by the preservation of high T1 signal on MRI all suggest this diagnosis. These conventional imaging findings are likely to remain important in distinguishing densely sclerotic metastatic foci with mild PSMA-targeted radiotracer uptake from Paget's disease.

It should be noted that this is only a single observational image report, with a second similar report only recently published (17). These findings will therefore need to be confirmed in other patients undergoing PSMA-targeted PET studies. Further, given the definitively Pagetoid appearance of the sacrum in this case, we did not believe it was necessary to confirm the findings by invasive means, leading to a lack of histologic evidence to support the presented conclusions.

In summary, PSMA-based PET/CT is a promising means of evaluating PCa in a variety of clinical contexts; however, as with almost any imaging modality, there are potential false-positive findings that can complicate the interpretation of these examinations. The uptake of PSMA-targeted agents in Paget's disease of bone is important to recognize as a potential false-positive finding of this imaging technique.

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Conflicts of Interest: M.G.P. is a coinventor of a US patent covering [18F]DCFPyL and as such is entitled to a portion of any licensing fees and royalties generated by this technology. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies.

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