Prostate-Specific Membrane Antigen (PSMA) Uptake in the Scrotum and Epididymis on PET-CT: When is it Pathological?

Abstract

Prostate cancer is the most common solid organ tumor in men and has been reported to metastasize to unusual sites such as the epididymis. The clinical standard for detecting recurrent disease is through positive emission tomography/computed tomography with the radiotracer ^{18}F-DCFPyL binding prostate-specific membrane antigen (PSMA) expressed by cancerous cells. Although PSMA can also be expressed physiologically, metastases are more likely to be intensely PSMA expressing and in a typical distribution depending on the extent of disease burden in the individual patient. A MEDLINE search revealed only three other case reports of isolated epididymal metastases from prostate cancer diagnosed with prostate-specific membrane antigen positron emission tomography–computed tomography. This case series comprising both metastatic and physiological PSMA expression in the epididymis provides a useful framework for the interpreting physician when the possibility of this rare but important finding is encountered in prostate cancer imaging.

Keywords: *Epididymal metastasis, epididymis, prostate cancer, prostate-specific membrane antigen positron emission tomography–computed tomography*

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Introduction

Prostate cancer is the most common solid organ tumor in men, with more than 1 million new cases reported worldwide annually.[1] Prostate cancer can metastasize to any part of the body, with the most common sites including lymph nodes, bones, lungs, liver, and adrenal glands. Several case series and reports have noted metastatic spread of prostate cancer to unusual sites such as the esophagus, eye, periureteric fat, testes, and epididymis.[2,3]

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein that has significantly elevated expression in prostate cancer cells, compared to background prostate parenchyma.[4] The development of radiotracer labeled molecules such as ^{18}F-DCFPyL, which selectively bind to the PSMA molecule, has allowed hybrid imaging PSMA positron emission tomography–computed tomography (PET-CT) techniques to emerge as a new clinical standard for the imaging, diagnosis, and staging of metastatic prostate cancer.[5] However, studies have also demonstrated the physiological uptake of PSMA at unusual sites.[6] Examining five cases, we present a series of characteristics to differentiate physiological epididymal uptake from epididymal prostate cancer metastasis detected by ^{18}F-DCFPyL-PSMA PET-CT.

Case Descriptions (1 and 2, Pathological Cases)

Case 1

A 73-year-old male presented with a painless right scrotal lump on a background of metastatic prostate adenocarcinoma and a rising serum prostate-specific antigen (PSA) level of 2.8 ug/L, 4 years after undergoing external beam radiotherapy (EBRT) and androgen deprivation therapy for Gleason 4 + 3 = 7 prostate adenocarcinoma. A scrotal ultrasound revealed a 16 mm × 14 mm lesion in the right epididymis, initially thought to represent phlegmonous change secondary to epididymitis. ^{18}F-DCFPyL-PSMA PET-CT revealed an intensely PSMA-expressing lesion in the right epididymis (SUVmax 12) and which was new from previous PSMA PET scans, suggesting a prostate cancer metastasis. [Figure 1] No other sites of metastatic disease were demonstrated. Retrospective review of the previous ultrasound in view of the findings on

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PSMA PET demonstrates a lesion compatible with an epididymal metastasis, as opposed to the initial diagnosis of epididymitis. The patient then underwent treatment with novel anti-androgen receptor therapy with subsequent reduction of PSA level, clinical reduction in palpable mass in the scrotum, and PSMA PET/CT showing resolution of the epididymal metastasis. Follow-up PSMA PET showed resolved uptake in the left common iliac node and right epididymis (SUVmax <2.0, less than background) and confirming metastatic foci, the patient had stabilized very low PSA at the last follow-up whilst on therapy (PSA <0.1 ug/L), which was at 18 months.

Case 2

A 77-year-old male presented with rising PSA level (PSA 1.1 ug/L), 2 years post robotic radical prostatectomy and pelvic salvage EBRT for Gleason 4 + 4 = 8 prostate adenocarcinoma (positive margin and seminal vesical invasion at resection). ^{18}F-DCFPyL-PSMA PET-CT showed a solitary and intensely PSMA-expressing (SUVmax 9) lesion in the left hemiscrotum. [Figure 2] Retrospectively, a faint focus of PSMA expression was seen in the same location on PSMA PET-CT performed 6 months earlier when the PSA level was 0.6 ug/L and initially interpreted as negative for the disease. Targeted ultrasound confirmed a small hypoechoic lesion within the left epididymis with associated color Doppler vascularity. Given a progressive lesion with anatomic correlate, this was interpreted as a solitary epididymal prostate cancer metastasis and systemic anti-androgen therapy was started. Following systemic therapy, the PSA level declined to <0.005 ug/L at the last measurement at 10-month follow-up.

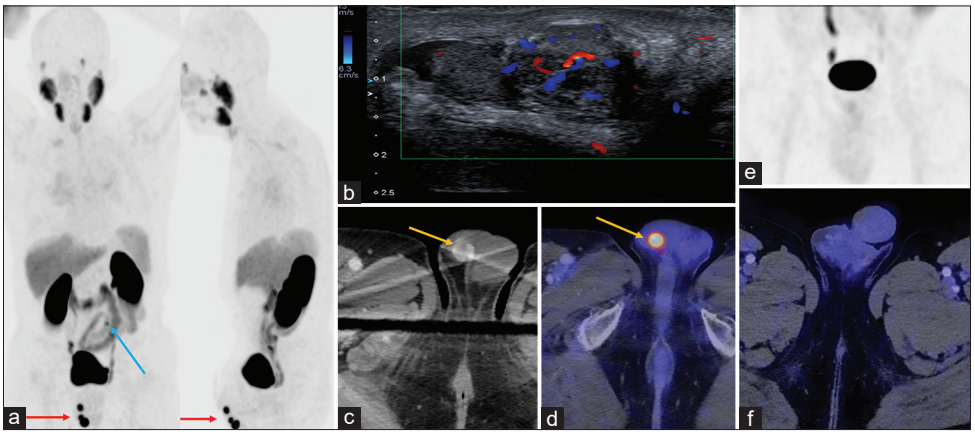

Figure 1: 73-year-old male prostate-specific membrane antigen (PSMA) positron emission tomography–computerized tomography (PET-CT) for biochemical recurrence (a) PSMA PET MIP imaging demonstrates three intensely PSMA expressing nodules (red arrow) within the right hemi-scrotum (on coronal and sagittal projection), as well as a moderately PSMA expressing left common iliac node (blue arrow). (b) Earlier scrotal ultrasound demonstrating a heterogeneously hypoechoic lesion within the right epididymis with associated vascularity, compatible with a metastatic deposit. (c) Axial contrast-enhanced CT: concordant enhancing soft-tissue lesion (yellow arrow) within the right hemi-scrotum, with intense uptake evident on fusion imaging (d). (e and f) Follow-up PSMA PET following anti-androgen therapy shows resolved uptake in the left common iliac node and right epididymis (SUVmax <2.0, less than background) and confirming metastatic foci

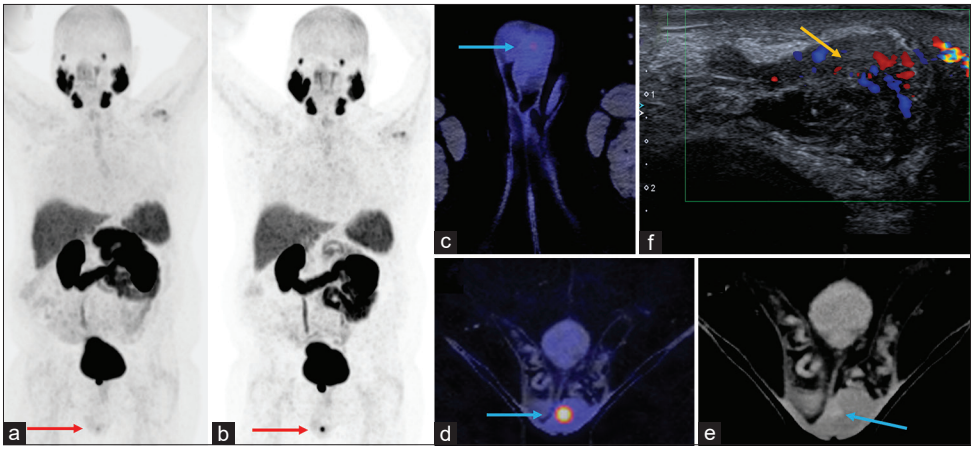

Figure 2: 77-year-old male prostate-specific membrane antigen (PSMA) positron emission tomography–computerized tomography (PET-CT) for biochemical recurrence (b) PSMA PET MIP imaging demonstrates a solitary intensely PSMA expressing focus (red arrow, SUVmax 9) within the left hemi-scrotum. Minor increased expression evident in a similar location (in retrospect) on the previous PET from 12 months prior (a). (c and d) Focal region of uptake within the left hemi-scrotum (blue arrow) on axial (c) and coronal (d) projection, with a concordant small enhancing lesion in this location on CT (e). (f) Small hypoechoic lesion within the left epididymis with associated color Doppler vascularity, compatible with a metastasis (yellow arrow)

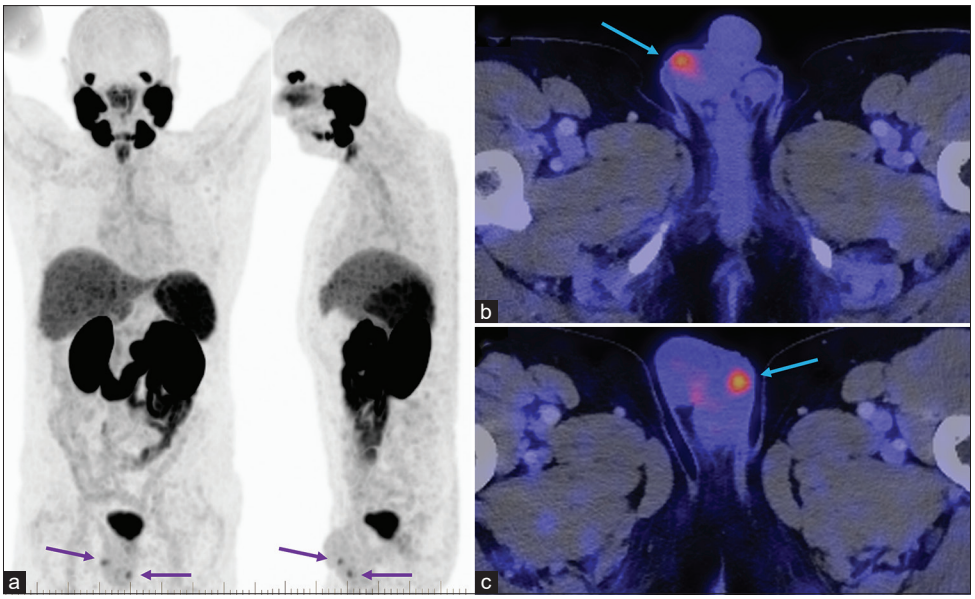

Figure 3: 62-year-old male restaging prostate-specific membrane antigen (PSMA)-positron emission tomography–computerized tomography (PET-CT) for biochemical recurrence (a) MIP imaging (coronal and sagittal projections) demonstrates bilateral small foci of mild PSMA expression (purple arrows) in the scrotum (SUVmax 3.6). The low level of uptake and bilaterality favors physiological uptake (supported by the absence of any identifiable lesions on a subsequent ultrasound). (b and c) Corresponding areas of mild focal PSMA expression (blue arrows) within the scrotum bilaterally on fusion PET-CT imaging

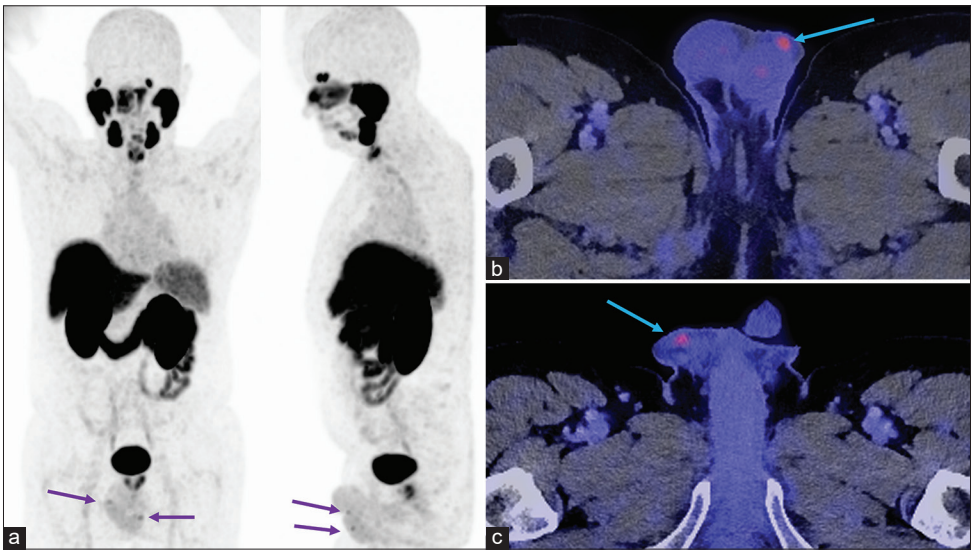

Figure 4: 69-year-old male prostate-specific membrane antigen (PSMA) positron emission tomography–computerized tomography (PET-CT) for prostate cancer staging (a) MIP imaging (coronal and sagittal projections) demonstrates two small foci of mild PSMA expression (purple arrows) in the scrotum bilaterally (SUVmax 4). (b and c) Corresponding areas of mild focal PSMA expression (blue arrows) within the scrotum bilaterally (including within the right epididymis (c) on fusion PET-CT imaging. The low level of uptake is in keeping with physiological PSMA expression (with no focal lesions identified on a subsequent ultrasound)

Case Descriptions (3, 4, and 5 Companion Cases of Physiological Expression)

Case 3

A 62-year-old male was imaged with PSMA PET/CT to evaluate biochemical recurrence (PSA level 0.5 ug/L) 3 years post robotic radical prostatectomy for Gleason 3 + 4 = 7 prostate adenocarcinoma. Mild PSMA expression in the scrotum (SUVmax 3.6) was seen and no disease was present elsewhere. [Figure 3] The low level of uptake and bilaterality, (i.e. symmetric pattern in both epidydmi) favors physiological uptake (also supported by the absence of any identifiable lesions on a subsequent ultrasound).

Case 4

A 69-year-old male was imaged with PSMA PET/CT to stage biopsy-proven multifocal Gleason 3 + 4 = 7 prostate cancer adenocarcinoma (PSA level 5.1 ug/L). Two small foci of mild PSMA uptake (SUVmax 4) were present in the bilateral scrotum/epididymis. [Figure 4] There was

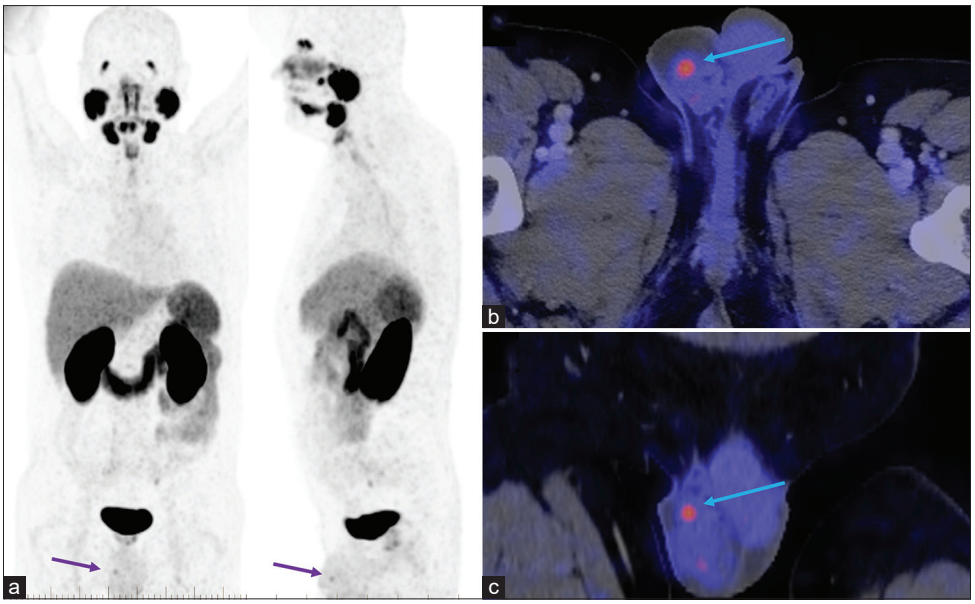

Figure 5: 60-year-old male prostate-specific membrane antigen (PSMA) positron emission tomography–computerized tomography (PET-CT) for prostate cancer staging (a) MIP (coronal and sagittal projections) demonstrate a small focus of low-grade tracer uptake (purple arrow) within the right hemi-scrotum, compatible with unilateral physiological PSMA expression. Axial fusion PET-CT shows a corresponding region of mild uptake (blue arrow) localizing to the epididymis on axial (b) and coronal (c) projection. This small focus of PSMA expression was stable on a 12-month follow-up PSMA-PET

Table 1: Summary of differentiating features between physiological versus pathological prostate-specific membrane antigen expression in the epididymis on positron emission tomography/computed tomography for prostate cancer

Physiological	Pathological
Bilateral symmetric pattern	Focal unilateral pattern
Relatively low-level PSMA expression intensity (SUVmax <3)	Relatively moderate to intense PSMA intensity (SUVmax >4, usually higher)
Hybrid contrast CT shows uniform nonnodular enhancement only, which is not striking on visual assessment	Correlating anatomical correlate on hybrid contrast-enhanced CT-in particular focal enhancing nodule on CT
No clinical findings on scrotal examination	Ultrasound correlate of hypoechoic nodule which shows color Doppler vascularity hyperemia

PSMA: Prostate-specific membrane antigen, CT: Computed tomography, SUVmax: Maximum standardized uptake value

no nodal or metastatic disease otherwise present (clinical stage thus N0M0). This was interpreted as physiological epididymal PSMA expression and the patient is now 2 years prostate prostatectomy with nondetectable PSA level/clinical remission.

Case 5

A 60-year-old male was imaged with PSMA PET/CT to stage biopsy-proven Gleason 3 + 3 = 6 prostate cancer adenocarcinoma (PSA level 4.5 ug/L). A unilateral single small focus of mild PSMA uptake (SUVmax 3.8) was present in the right scrotum/epididymis. [Figure 5] There was no nodal or metastatic disease otherwise present (clinical stage thus N0M0). Given the unilateral scrotal uptake, scrotal ultrasound was recommended, which excluded any focal lesion. The patient had 12-month surveillance PSMA PET/CT proving the right scrotal lesion was stable (active surveillance strategy adopted over prostatectomy given only Gleason 3 + 3 = 6 disease).

Discussion

In this article, we present two cases of isolated epididymal metastasis from prostate cancer identified on hybrid ^{18}F-DCFPyL-PSMA PET-CT imaging in the context of rising PSA levels. To the best of our knowledge, only 3 other cases of epididymal prostate cancer metastases diagnosed by PSMA PET have been reported in the literature.[7-9] Epididymal tumors are uncommon, with 94% of lesions found to be benign.[10] Metastatic tumors to the epididymis are exceedingly rare, with the first case of metastatic prostate cancer to the epididymis reported in 1944 and less than 30 cases reported in the literature to date.[9,11-13] Proposed theories regarding dissemination routes include arterial embolization, retrograde venous extension, lymphatic extension, or retrograde intraluminal spread through the vas deferens.[3,14] DCFPyL PSMA ligand has propensity to bind to PSMA receptors expressed on the endothelium of the tumor microenvironment. Subsequently, it is important to differentiate these from physiological uptake on F^{18}-DCFPyL-PSMA PET-CT.

We also present three cases of physiological uptake of PSMA, similar to those described previously by Maliha *et al*.[6] Compared to metastatic lesions, these areas are more likely to be less intensely PSMA avid, bilateral, and without focal enhancing mass-like/nodule-like lesion on contrast-enhanced CT acquired with PSMA PET. Interestingly, Maliha *et al*. propose their findings of physiological activity are most likely due to the use of digital PET/CT. All current cases were imaged on the same PET/CT scanner, a Siemens biograph mCT manufactured/installed in 2018 with time-of-flight correction and the difference in clinical experience is interesting as we do not observe such a high rate of physiological expression. Maliha *et al*. also found that physiologic epididymal uptake of PSMA is common on PSMA PET-CT, particularly in patients with serum testosterone levels >5 nmol/L.[6] Our findings of pathological epididymal uptake are useful as companion cases to the physiological expression spectrum. Activated macrophages within the epididymis express high levels of folic acid receptors, concentrating PSMA-targeted tracers.[15] In addition, there is a high concentration of androgen receptors on the proximal epididymis which may explain the testosterone-mediated mechanism of PSMA uptake.[16] In our cases showing the spectrum of physiological PSMA distribution in the scrotum, we find physiological expression is more likely where there is less intense activity (SUVmax <5), bilateral distribution, and the lack of concordant enhancing nodule on contrast-enhanced CT (CECT). Case 5 did show unilateral PSMA uptake in the scrotum, however, this was relatively mild initially, and the clinical decision was made for follow-up PSMA PET/CT, which proved 12-month stability and, therefore, confirming physiological expression. Thus, in equivocal cases, follow-up PSMA PET/CT imaging or clinical surveillance may still be necessary.

It is vital for the clinician to maintain a high index of suspicion for the potential of metastatic disease from prostate cancer at unusual sites (particularly in the context of concerning clinical factors such as a rising PSA), as evidenced in case 1 as the initial incorrect diagnosis of epididymitis on scrotal ultrasound. These cases highlight the importance of PSMA PET-CT as an imperative whole-body imaging modality for accurate diagnosis of uncommon and rare metastatic lesions. The management of the patient whether a prostate cancer metastasis is to the epididymis versus the test itself, would in most cases be similar as these would constitute distant disease and would necessitate systemic therapy (either anti-androgen therapy or second, third-line therapies depending on the clinical course). There may be situations, in which the urologist or oncologist may offer surgical resection if a scrotal metastasis was a solitary lesion, but in our case 2, this was not considered indicated. Helpful differentiating features are summarized in Table 1.

PSMA PET/CT was performed as hybrid imaging with contemporaneous CECT for all our cases. This is routine clinical practice in our institution. Our cases highlight the importance of hybrid CECT in aiding the interpretation of PSMA PET images. CECT enabled anatomical resolution and assessment of enhancement characteristics of images of the scrotum to enable diagnosis. Testicular metastasis is associated with a high Gleason score (≥7), although the prognostic impact of these rare epididymal metastases is unknown.[17] Early and timely detection of single site or oligometastatic disease using ^{18}F-DCFPyL-PSMA PET-CT enables metastasis-directed therapy which would positively steer progression-free survival and outcome.[7]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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