Radiology Case Reports 19 (2024) 4122–4126

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

A peculiar distribution on ^{18}F-DCFPyL-PSMA PET scan for a patient with prostate cancer and protein S deficiency ☆

Vaisnavi Thirugnanasundralingam, Shannon McGrath, Jay Roberts, Niall Corcoran*

Department of Urology, Western Health, Footscray, VIC, Australia

ARTICLE INFO

Article history:
Received 15 August 2023
Revised 21 May 2024
Accepted 6 June 2024

Keywords:
Prostate cancer
PSMA-PET
PSMA
Protein S deficiency

ABSTRACT

A 54-year-old male with biopsy-confirmed Gleason 4+4 prostate cancer underwent ^{18}F-DCFPyL-PSMA PET scan to identify occult metastatic disease. This scan revealed abnormal radionuclide uptake not only in the prostate but also within the patient's vasculature. The scan was repeated after a week with a separate tracer batch, yielding the same result. Standard staging was performed using computed tomography and a Technetium-99 bone scan, revealing no metastatic disease. The patient's protein S deficiency is thought to have caused this peculiar tracer distribution. With the advent of PSMA PET for staging in prostate cancer, clinicians must be familiar with situations that may render unusual results.

Introduction

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein that is overexpressed on prostate cancer cells. Additionally, PSMA expression has been detected in various tissues, including the proximal tubules of the kidney, small intestine, and ganglia of the nervous system, often associated with neo-vascularisation. Its heightened expression in prostate cancer is key to its utility in identifying occult prostate cancer, even at low PSA levels, and it is increasingly utilised in the identification of metastasis in patients with high-risk prostate cancer and in those with a biochemical recurrence following radical treatment, with high sensitivity and specificity (85% and 98% respectively.)

Despite its high specificity, there are reports of unusual PSMA PET tracer distribution patterns. This is the first case, to our knowledge, wherein a patient has had PSMA tracer distributed not only within their prostate but also, remarkably, within their vasculature in the context of prostate cancer and protein S deficiency.

PSMA PET has garnered popularity among Urologists as a staging tool for high-risk prostate cancer and to identify early cases of metastasis/regional invasion in cases of biochemical recurrence following radical treatment of prostate cancer. Only recently has the Australian Government announced

☆ Competing Interests: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

* Corresponding author.
E-mail address: vaisnaviuthiru@gmail.com (V. Thirugnanasundralingam).

https://doi.org/10.1016/j.radcr.2024.06.021

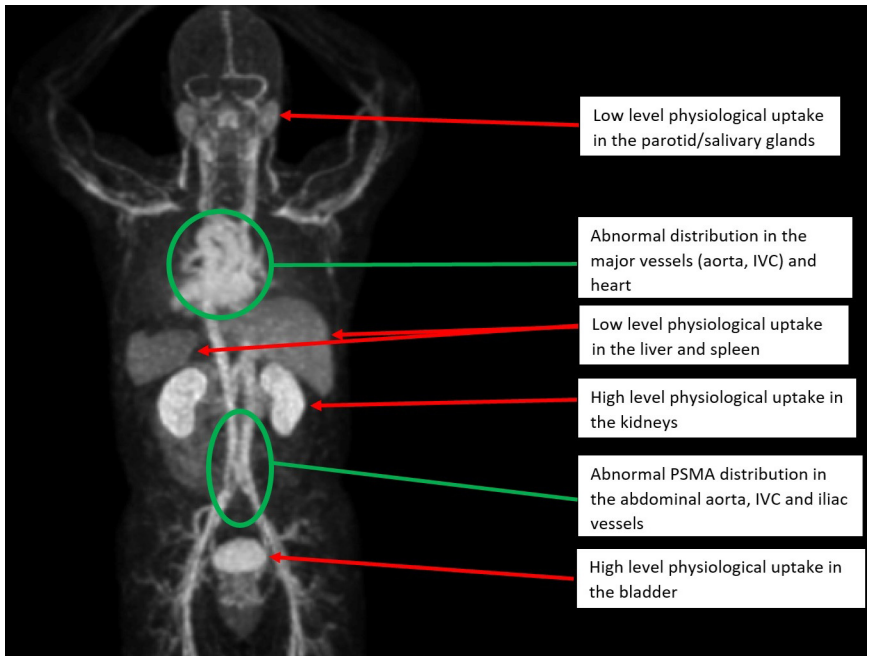

Fig. 1 – A coronal section of AM's PSMA PET scan, demonstrating grossly abnormal uptake by the vasculature, as well as physiological avidity seen in the salivary glands, kidneys, liver, spleen, small intestine and bladder, and within the prostate, as expected in the context of biopsy confirmed Gleason 4=$ prostate cancer.

funding for whole-body PSMA PET scans for eligible patients with prostate cancer, indicating a growing accessibility and utilization of this imaging modality. With its increasing availability and use, we are likely to encounter other such examples of unique tracer distributions. Where possible, these instances should be highlighted in medical literature to raise awareness as we explore this new radiological modality.

Case presentation

An asymptomatic male in his 50s was referred to the Urology clinic for further investigation of his elevated Prostate Specific Antigen (PSA) level of 4.1 μg/L. He underwent transperineal prostate biopsy revealing Gleason 4+4 prostate acinar adenocarcinoma.

His medical history was significant for gastro-oesophageal reflux disease and protein S deficiency. His only regular medication was esomeprazole. Protein S deficiency was diagnosed by a Haematologist when AM was in his 40s, after several of his female relatives had been diagnosed with the condition. Although his female relatives had suffered from instances of pulmonary embolism and deep venous thrombosis, AM himself had never had any venous thromboembolic events and was not advised to take any anticoagulants or antiplatelet agents.

Following his biopsy result which demonstrated high-risk prostate cancer, AM went on to have a staging Prostate Specific Membrane Antigen (PSMA) positron emission tomography (PET) scan using radiotracer ^{18}F-DCPFyL to identify occult metastatic disease. The PSMA PET scan was performed contemporaneously with a low dose contrast-enhanced CT utilising 40 mL of iodinated contrast given intravenously to assist with anatomic correlation (and to opacify the ureters). AM was scanned 111 minutes after administration of 189 MBq of ^{18}F-DCPFyL-PSMA tracer.

The tracer material was distributed within the AM's vasculature as well as in the prostate and other areas of expected physiological avidity (kidneys (Fig. 4), liver (Fig. 3), small intestine, salivary glands). A different patient who had a PSMA PET scan on the same day, using the tracer from the same batch, had good image quality. AM remained asymptomatic and was discharged home.

One week following this, AM returned for a second PSMA PET scan. This time, he was scanned following the administration of 173 MBq of ^{18}F-DCFPyL-PSM at the following intervals: 30 seconds, 300 seconds, 119 minutes, and 4 hours.

Once again, the tracer was unusually distributed in his vascular system (in addition to within the prostate and within areas of expected physiological avidity), which persisted even at the 4-hour post-tracer administration mark. Figures 1-5 demonstrate unusual PSMA distribution in large arteries and veins (Fig. 2), as well as in organs with highly vascularised parenchyma such as the liver (Fig. 3). There is also less intense physiological PSMA avidity noted in the salivary glands, kidneys (Fig. 4), liver, spleen, small intestine and bladder (Fig. 1). Finally, there was PSMA avidity as expected within AM's prostate. (Fig. 1 and 5). AM remained well and was discharged home.

Alternative staging with computed tomography and a whole-body bone scan (utilising 864 MBq of Technetium-99 tracer) was performed revealing no evidence of metastatic disease.

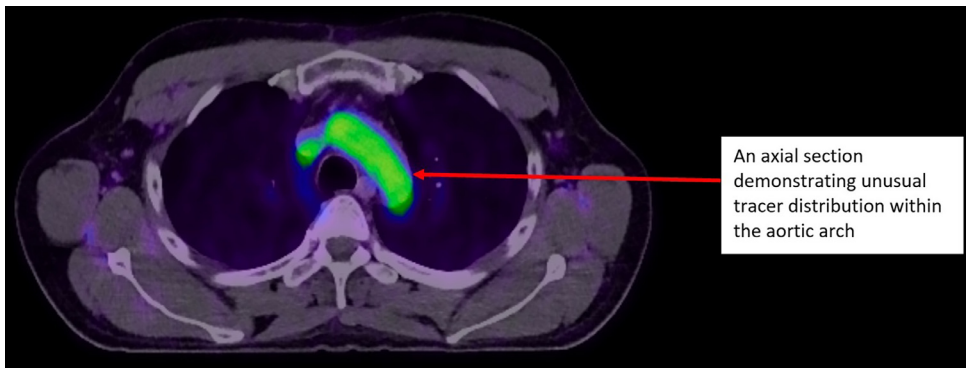

Fig. 2 – An axial section of AM's PSMA PET scan demonstrating radionuclide within the aortic arch.

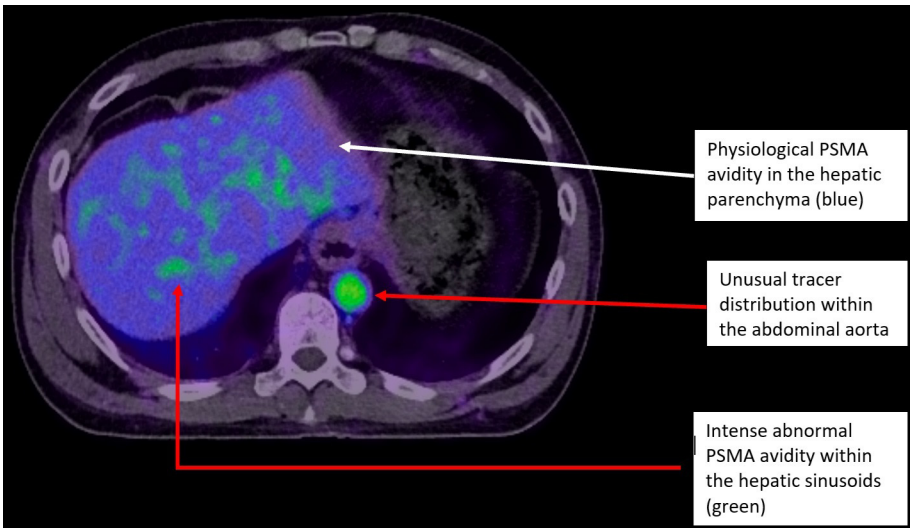

Fig. 3 – An axial section of AM's PSMA PET scan demonstrating intense tracer presence (green) within the hepatic sinusoids, abdominal aorta and inferior vena cava. There is also less intense, likely background physiological uptake (blue) by the hepatic parenchymal tissue.

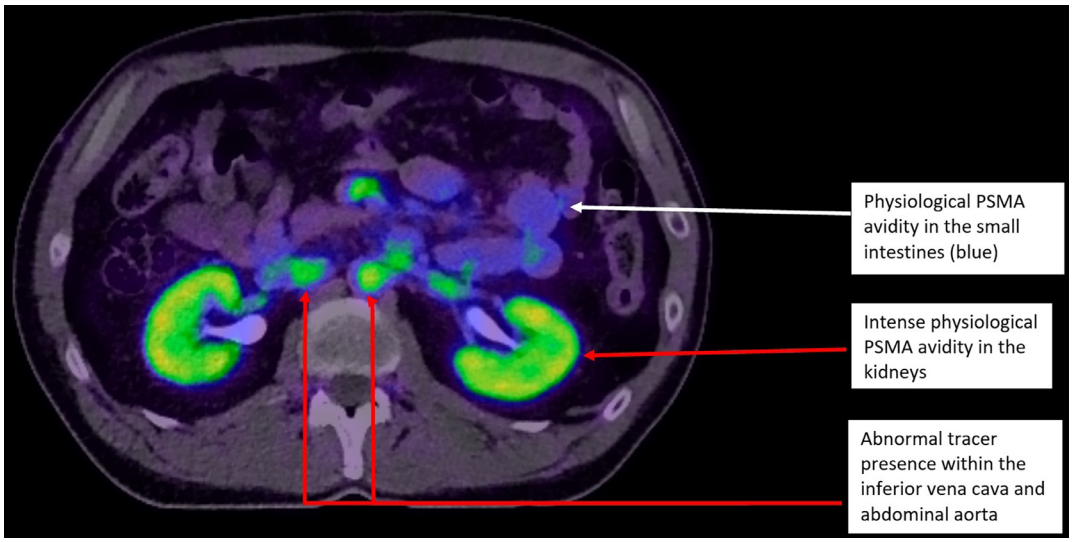

Fig. 4 – An axial section of AM's PSMA PET scan demonstrating tracer distribution in the renal parenchyma, inferior vena cava and abdominal aorta. There is also background less intense physiological uptake by the small intestines (blue).

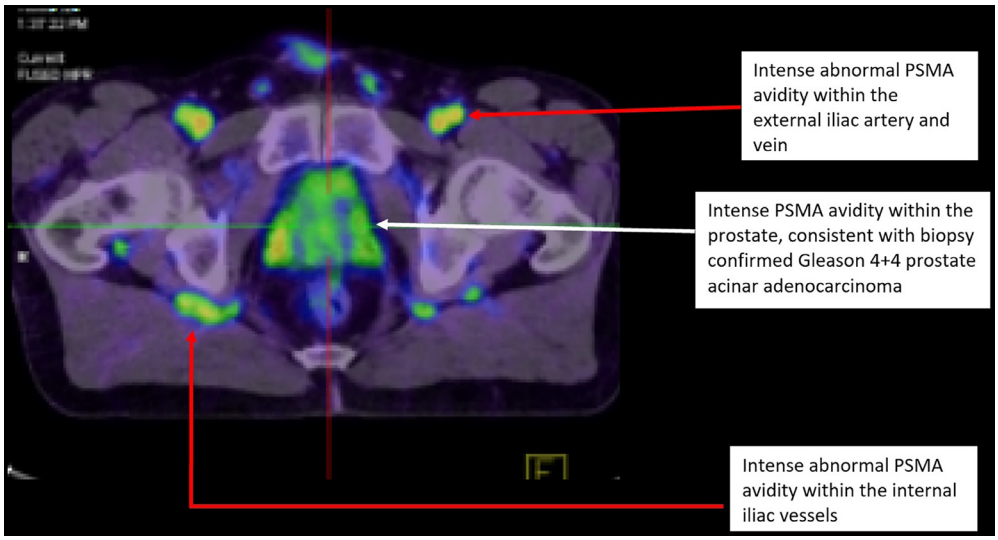

Fig. 5 – An axial section of AM's PSMA PET scan showing the prostate, which has intense PSMA avidity as expected, given his known biopsy confirmed Gleason 4+4 prostate cancer. There is also radionuclide distribution in his vasculature – bilateral femoral arteries, veins, iliac veins and arteries and their branches.

We attribute AM's abnormal ^{18}F-DCFPyL-PSMA PET scan results to his protein S deficiency.

Outcome and Follow-up

AM remained well after each PSMA PET scan and was safely discharged home. He also underwent conventional CT and bone scan staging, which revealed no evidence of metastatic disease. Finally, AM underwent laparoscopic radical prostatectomy and had an uneventful recovery from this. Final histopathology confirmed Gleason 4+4 prostatic acinar adenocarcinoma, which was resected with clear margins. He continues to be followed up in the Urology Outpatient Clinic.

Discussion

PSMA is a transmembrane glycoprotein, and its extracellular component is the target for PSMA ligand/tracer imaging [1]. There are many different PSMA tracers, of which ^{18}F-DCFPyL is 1 [1]. PSMA is internalized by a clathrin dependent endocytic mechanism, mediated by a specific sequence of amino acids found on its intracellular component (cytoplasmic tail) [2,3], which is currently under investigation as a potential target for the development of prostate cancer cell specific targeted immunotherapy [2,3].

Key to a successful PSMA-PET scan is ensuring the radiolabelled tracer ligand (in this case, ^{18}F-DCFPyL) binds to the target PSMA expressed by prostate cancer cells, triggering internalisation of the tracer [4] (ie, the tracer has to bind to PSMA and enter the cell).

Protein S is secreted predominantly by endothelial cells, megakaryocytes and hepatocytes [4] and has numerous roles including: preventing clot formation, acting as a cofactor for activated protein C and most notably; acting as a ligand for cell-surface receptors with intrinsic protein-tyrosine kinase activity [4,5]. Protein S is critical in the activation of intracellular signalling cascades via specific cell surface receptors and can transduce a variety of signals including those for cell survival, metastasis, angiogenesis and apoptosis [4,5].

There are over 200 different mutations of protein S that have been discovered, all of which cause varying degrees of protein dysfunction – and clinically, a prothrombotic state [4]. We postulate that owing to its role in signal transduction, protein S is implicated in the intracellular uptake of the ^{18}F-DCFPyL radionuclide. Consequently, in our patient who had protein S deficiency, the tracer material was unable to be sufficiently 'offloaded' from plasma to the PSMA target on prostate cancer cells, producing the peculiar distribution seen where considerable tracer material remained within AM's vasculature.

There have been multiple case reports of non-prostatic malignancies [6–8], benign tumors [9,10], bone-related conditions [11], non-prostatic inflammatory/infectious conditions [12–14] and recent prostate/pelvic surgery causing unusual PSMA-avidity [15]. Physiological PSMA uptake is observed in glandular tissue (lacrimal, parotid, submandibular glands), small intestine, kidneys, liver, spleen and bladder [16]. Endothelial PSMA expression is also evident in non-prostatic solid tumors with neovascularisation, providing a likely explanation for the observed PSMA avidity in both benign and malignant tumors [17]. Bony conditions including osteomyelitis and myelodysplasia can also demonstrate PSMA avidity, likely due to angiogenesis, and further investigations with complementary imaging modalities may be necessary [15]. It is crucial for clinicians to familiarise themselves with tissues exhibiting physiological PSMA avidity, and to initiate additional investigations in cases of atypical PSMA distribution. A thorough history and examination are imperative in interpreting such results.

To our knowledge, this case report represents the first documentation of tracer distribution within the vasculature in the context of protein S deficiency. Further research is warranted to validate the role of protein S in the binding and cellular signalling of PSMA tracer.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors did not use any Generative AI or AI-assisted technologies. The authors take full responsibility for the content of the publication.

Patient consent

I, author of the case report entitled "**A peculiar distribution on ^{18}F-DCFPyL-PSMA PET scan for a patient with prostate cancer and protein S deficiency.**" confirm that the patient involved in this case report provided written informed consent for their case to be published.

REFERENCES

[1] Will L, Sonni I, Kopka K, Kratochwil C, Giesel F, Haberkorn U. Radiolabeled prostate-specific membrane antigen small-molecule inhibitors. Q J Nucl Med Mol Imaging 2017;61:168–80. doi:10.23736/s1824-4785.17.02977-6.

[2] Rajasekaran SA, Anilkumar G, Oshima E, Bowie JU, Liu H, Heston W, et al. A novel cytoplasmic tail MXXXL motif mediates the internalization of prostate-specific membrane antigen. Mol Biol Cell 2003;14(12):4835–45. doi:10.1091/mbc.e02-11-0731.

[3] Liu H, Rajasekaran AK, Moy P, Xia Y, Kim S, Navarro V, et al. Constitutive and antibody-induced internalization of prostate-specific membrane antigen. Cancer Res 1998;58:4055–60.

[4] Pilli VS, Plautz W, Majumder R. The journey of protein s from an anticoagulant to a signaling molecule. JSM Biochem Mol Biol 2016;3:1014–15.

[5] Stitt TN, Conn G, Gore M, Lai C, Bruno J, Radzlejewski C, et al. The anticoagulation factor protein S and its relative, Gas6, are ligands for the Tyro 3/Axl family of receptor tyrosine kinases. Cell 1995;80:661–70. doi:10.1016/0092-8674(95)90520-0.

[6] Malik D, Mittal BR, Kumar R, et al. Incidental detection of tracer avidity in liposarcoma on 68Ga-labeled prostate-specific membrane antigen PET/CT. Clin Nucl Med 2018;43:e334–5. doi:10.1097/rlu.0000000000002189.

[7] Parihar AS, Vadi SK, Mittal BR, Kumar R, Bal A, Singh S. 68Ga-PSMA-HBED-CC-avid synchronous urinary bladder paraganglioma in a patient with metastatic prostate carcinoma. Clin Nucl Med 2018;43:e329–30. doi:10.1097/rlu.0000000000002172.

[8] Vaz S, Oliveira C, Castanheira JC, Silva AF, Costa DC. Gastric GIST incidentally detected on 68Ga-PSMA-PET/CT: correlation between functional imaging and histology. Clin Nucl Med 2018;43:e488–91. doi:10.1097/rlu.0000000000002347.

[9] Ahuja A, Taneja S, Thorat K, Jena A. 68Ga-Prostate-Specific membrane antigen-avid tubercular lesions mimicking prostate cancer metastasis on simultaneous prostate-specific membrane antigen PET/MRI. Clin Nucl Med 2017;42:e509–10. doi:10.1097/rlu.0000000000001874.

[10] Kanthan GL, Izard MA, Emmett L, Hsiao E, Schembri GP. Schwannoma showing avid uptake on 68Ga-PSMA-HBED-CC PET/CT. Clin Nucl Med 2016;41:703–4. doi:10.1097/rlu.0000000000001281.

[11] Jochumsen MR, Dias AH, Bouchelouche K. Benign traumatic rib fracture: a potential pitfall on 68ga-prostate-specific membrane antigen PET/CT for prostate cancer. Clin Nucl Med 2018;43:38–40. doi:10.1097/rlu.0000000000001871.

[12] McGuiness M, Sounness B. 68Ga-PSMA-Ligand PET/CT Uptake in Anthracosilicosis. Clin Nucl Med 2017;42:e431–2. doi:10.1097/rlu.0000000000001782.

[13] Huang K, Baur AD, Furth C. Prostate-specific membrane antigen-positive manifestations of chronic beryllium lung disease. Clin Nucl Med 2019;44:64–5. doi:10.1097/rlu.0000000000002323.

[14] Vadi SK, Kumar R, Singh H, Singh SK, Mittal BR. 68Ga-prostate-specific membrane antigen expression in neurocysticercosis lesions in a patient with prostate carcinoma. Clin Nucl Med 2018;43:e122–4. doi:10.1097/rlu.0000000000001990.

[15] de Galiza Barbosa F, Queiroz MA, Nunes RF, Costa LB, Zaniboni EC, Marin JFG, et al. Nonprostatic diseases on PSMA PET imaging: a spectrum of benign and malignant findings. Cancer Imaging 2020;20:3–5. doi:10.1186/s40644-020-00300-7.

[16] Hofman MS, Hicks RJ, Maurer T, Eiber M. Prostate-specific membrane antigen PET: clinical utility in prostate cancer, normal patterns, pearls, and pitfalls. Radiographics 2018;38:200–17. doi:10.1148/rg.2018170108.

[17] Chang SS, O'Keefe DS, Bacich DJ, Reuter VE, Heston WD, Gaudin PB. Prostate-specific membrane antigen is produced in tumor-associated neovasculature. Clin Cancer Res 1999;5:2674–81.