Unusual Uptake of Prostate Specific Tracer ^{68}Ga -PSMA-HBED-CC in a Benign Thyroid Nodule

Nishikant Avinash Damle¹ · Madhavi Tripathi¹ · Partha Sarathi Chakraborty¹ ·
Manas Kumar Sahoo¹ · Chandrasekhar Bal¹ · Shipra Aggarwal² · Geetanjali Arora¹ ·
Praveen Kumar¹ · Rajeev Kumar¹ · Ravikant Gupta¹

Received: 19 March 2015 / Revised: 12 February 2016 / Accepted: 17 February 2016 / Published online: 22 March 2016
© Korean Society of Nuclear Medicine 2016

Abstract ^{68}Ga -Prostate specific membrane antigen- N,N' -bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine- N,N' -diacetic acid- positron emission tomography/computed tomography or ^{68}Ga -HBED-CC-PSMA PET/CT, popularly known as PSMA PET/CT, is able to detect a small volume of recurrent prostate carcinoma (PC) when there is a prostate specific antigen (PSA) rise on follow-up after prostatectomy or other definitive treatment for PC. The use of PSMA PET/CT in the initial staging in PC is uncertain at this time. Clinical studies are underway to define its exact role in the management of the disease. At the same time it is important to be aware of unexpected sites of uptake of this ligand. We present here the case of a 62-year-old male patient who underwent prostatectomy for adenocarcinoma prostate. He also had a long-standing left solitary thyroid nodule (STN). Four months after surgery, he had a rising trend in serum PSA levels on three occasions, but the absolute value was less than 4 at all times. He underwent a ^{68}Ga -PSMA-HBED-CC PET/CT, but it did not reveal any recurrent/metastatic site of disease. However, there was increased tracer uptake in the left STN.

Fine needle aspiration cytology revealed features of atypia of undetermined significance, Bethesda category III. The patient underwent a left hemithyroidectomy and the histopathology showed features of a follicular adenoma.

Keywords ^{68}Ga Gallium · PET/CT · Prostate carcinoma · PSMA

Introduction

^{68}Ga -Prostate specific membrane antigen- N,N' -bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine- N,N' -diacetic acid- positron emission tomography/computed tomography or ^{68}Ga -HBED-CC-PSMA PET/CT has been shown to be sensitive in detection of recurrent prostate carcinoma (PC) when there is a rising PSA on follow-up after prostatectomy. Clinical studies are underway to define its exact role in the management of the disease. At the same time it is important to be aware of unexpected sites of uptake of this tracer. We present here the case of a 62-year-old male patient who underwent

✉ Nishikant Avinash Damle
nkantdamle@gmail.com

Madhavi Tripathi
madhavi.dave.97@gmail.com

Partha Sarathi Chakraborty
parthasarathi247@gmail.com

Manas Kumar Sahoo
dmksahoo@gmail.com

Chandrasekhar Bal
drcsbal@gmail.com

Shipra Aggarwal
drshipra0902@gmail.com

Geetanjali Arora
a.geetanjali@gmail.com

Praveen Kumar
pkgaiims@gmail.com

Rajeev Kumar
rajeevrajaiims@gmail.com

Ravikant Gupta
dr.ravi.kant.gupta@hotmail.com

¹ Department of Nuclear Medicine, A.I.I.M.S, New Delhi, India

² Department of Pathology, A.I.I.M.S, New Delhi, India

prostatectomy for adenocarcinoma prostate. Unusual uptake of the PET tracer was seen in the ^{68}Ga -PSMA-HBED-CC PET/CT in a long-standing solitary thyroid nodule (STN), which turned out to be a follicular adenoma. The tracer used in our study is a prostate specific membrane antigen (PSMA)-selective dimer, labeled with ^{68}Ga complex of *N,N'*-bis[2-hydroxy-5-(carboxyethyl)benzyl]ethylenediamine-*N,N'*-diacetic acid (HBED-CC) [1]. In this tracer HBED-CC contributes intrinsically to the PSMA binding of the Glu-urea-Lys(Ahx) pharmacophore [2].

Case Report

A 62-year-old male patient who underwent prostatectomy 4 months ago and had documented undetectable PSA presented with a rising PSA on three consecutive occasions. The last PSA value was 3.9 ng/mL. He underwent ^{68}Ga -PSMA-HBED-CC PET/CT after injection of 3 mCi of the tracer in a non-fasting state, with whole body non-contrast PET/CT performed on a Biograph mCT scanner which did not show any site of recurrence or metastases. He also had a left STN in the last 17 years, which showed, increased uptake of the tracer. The figure shows increased uptake of the tracer in a hypodense nodule in the left lobe of thyroid (Fig. 1b, c) correlated with CT (Fig. 1a). The nodule also showed some calcification. The rest of the thyroid, which appeared morphologically normal, did not show tracer uptake. FNAC performed using a 23G needle from the thyroid nodule yielded moderate cellular smears. No colloid was identified in the background. The follicular cells were arranged in clusters with focal microfollicular pattern. Some of the follicles had a thick colloid in the center. Focal nucleomegaly and overlapping along with occasional nuclear grooves were also noted,

however, no pseudo-inclusion was seen. Hence, a diagnosis of “atypia of undetermined significance” (Bethesda category III) was given. In view of the above FNAC report and considering his elderly age, and male gender, the patient was advised a hemi-thyroidectomy.

Sections examined from the hemi-thyroidectomy specimen showed a well-encapsulated follicular neoplasm. The tumor cells arranged in variably sized follicles had dark-staining round nuclei. Nuclear features characteristic of papillary thyroid carcinoma including nuclear clearing, pseudo-inclusions, significant nuclear enlargement or overlapping were lacking, although an occasional cell did show nuclear groove. No psammoma body or capsular invasion was found and a final diagnosis of follicular adenoma was rendered (Fig. 2).

Discussion

PC is the leading cause of cancer in males worldwide and its incidence is increasing [3]. Generator based ^{68}Ga -PSMA-HBED-CC is a new addition to the list of novel PET tracers available for PC imaging. PSMA is a cell surface protein (membrane type zinc protease also called glutamate carboxy-peptidase II) expressed in prostate cells physiologically and is overexpressed in PC [4]. Enhanced PSMA expression is seen in poorly differentiated, metastatic, and hormone refractory cancers [5, 6]. The major advantage of this tracer is that it is a very sensitive modality for the detection of recurrent lesions and gives a high target-to-background ratio in metastatic sites even at low levels of PSA [7]. The most useful role of this tracer has been in cases of biochemical recurrence [8]. ^{68}Ga -PSMA-HBED-CC has been compared to ^{11}C -fluoromethylcholine in the diagnosis of PC and has been found to be more sensitive in the diagnosis of lymph node,

Fig. 1 Fused PET/CT (a) and transaxial CT (b) image showing a hypodense nodule (arrow) with peripheral calcification and increased ^{68}Ga -PSMA-HBED-CC uptake. MIP (c) image showing physiological distribution of the tracer along with uptake in the left thyroid nodule (arrow)

Fig. 2 **a, b** Photomicrographs of aspiration cytology showing fragments of tumor with cells arranged focally as microfollicles (*short arrow*) some with thick colloid in the lumen. Some of the tumor cells shows mild nuclear enlargement, overlapping and grooves (*long arrow*) (**a**

Papanicolaou stain $\times 200$; **b** MGG $\times 200$). **c, d** A well-encapsulated lesion with cells arranged in closely packed follicles. The nuclei are dark staining without significant nucleomegaly/nuclear overlapping (**c** H&E $\times 40$; **d** H&E $\times 200$)

central bone, and liver metastases [9]. Biodistribution studies have revealed uptake of the radiotracer in the lacrimal glands, salivary glands, liver, spleen, kidneys, small and large bowel besides lesions suspicious for PC [10]. Atypical uptake of this tracer has been reported in the celiac ganglion mimicking lymph nodes [11]. Thyroid incidentalomas are sometimes found in patients undergoing FDG PET/CT for unrelated causes and a significant proportion of them have been shown to harbor malignancy [12]. Recently the uptake of ^{68}Ga -PSMA-HBED-CC has been reported in differentiated thyroid cancer by Verburg et al. in nodal and pulmonary metastases in a patient with poorly differentiated thyroid carcinoma that was radioiodine negative [13]. Tracer uptake has also been shown in metastatic renal cell carcinoma by Demirci et al. [14]. An early study by Chang et al. showed that anti-PSMA monoclonal antibodies react strongly with neovasculature of various tumors including clear renal cell carcinoma, transitional cell carcinoma of the urinary bladder, testicular embryonal carcinoma, colonic adenocarcinoma, neuroendocrine carcinoma, glioblastoma multiforme, malignant melanoma, pancreatic duct carcinoma, non-small cell lung carcinoma, soft tissue sarcoma, breast carcinoma, and prostatic adenocarcinoma [15]. Another early study also reported PSMA immunoreactivity in cells of the duodenal mucosa, renal tubules, neuroendocrine cells in the colonic crypts, apart from a few malignancies like renal cell carcinoma and colonic adenocarcinomas [7]. To the best of our knowledge, this is the first case in literature where ^{68}Ga -PSMA-HBED-CC uptake has been demonstrated in a follicular adenoma of the thyroid. Since this

is an upcoming tracer the knowledge of its uptake at atypical sites may help the reporting physician to be alert regarding incidental sites of uptake.

Compliance with Ethical Standards

Conflict of Interest Nishikant Avinash Damle, Madhavi Tripathi, Partha Sarathi Chakraborty, Manas Kumar Sahoo, Chandrasekhar Bal, Shipra Aggarwal, Geetanjali Arora, Praveen Kumar, Rajeev Kumar, and Ravikant Gupta declare no conflict of interest.

Ethical Statement The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The subject in the study gave written informed consent.

The manuscript has not been published before, is not under consideration for publication anywhere else and has been approved by all co-authors.

References

- Schäfer M, Bauder-Wüst U, Leotta K, Zoller F, Mier W, Haberkorn U, et al. A dimerized urea-based inhibitor of the prostate-specific membrane antigen for ^{68}Ga -PET imaging of prostate cancer. *EJNMMI Res.* 2012;2:23.
- Eder M, Neels O, Müller M, Bauder-Wüst U, Remde Y, Schäfer M, et al. Novel preclinical and radiopharmaceutical aspects of ^{68}Ga -PSMA-HBED-CC: a new PET tracer for imaging of prostate cancer. *Pharmaceuticals.* 2014;7:779–96.

3. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics. *CA Cancer J Clin*. 2014;64:9–29.
4. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. *Clin Cancer Res*. 1997;3:81–5.
5. Schülke N, Varlamova OA, Donovan GP, Ma D, Gardner JP, Morrissey DM, et al. The homodimer of prostate-specific membrane antigen is a functional target for cancer therapy. *Proc Natl Acad Sci U S A*. 2003;100:12590–5.
6. Hellwig D, Moosbauer J, Eilles C. ^{68}Ga -PSMA PET/CT for prostate cancer. *Aktuelle Urol*. 2014;45:457–63.
7. Chakraborty PS, Tripathi M, Agarwal KK, Kumar R, Vijay MK, Bal C. Metastatic poorly differentiated prostatic carcinoma with neuroendocrine differentiation: negative on ^{68}Ga -PSMA PET/CT. *Clin Nucl Med*. 2015;40:163–6.
8. Bouchelouche K, Turkbey B, Choyke P, Capala J. Imaging prostate cancer: an update on positron emission tomography and magnetic resonance imaging. *Curr Urol Rep*. 2010;11:180–90.
9. Afshar-Oromieh A, Haberkorn U, Eder M, Eisenhut M, Zechmann CM. ^{68}Ga -Gallium-labelled PSMA ligand as superior PET tracer for diagnosis of prostate cancer: comparison with ^{18}F -FECH. *Eur J Nucl Med Mol Imaging*. 2012;39:1085–6.
10. Afshar-Oromieh A, Malcher A, Eder M, Eisenhut M, Linhart HG, Hadaschik BA, et al. PET imaging with a ^{68}Ga -gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. *Eur J Nucl Med Mol Imaging*. 2013;40:486–95.
11. Krohn T, Verburg FA, Pufe T, Neuhuber W, Vogg A, Heinzel A, et al. ^{68}Ga -PSMA-HBED uptake mimicking lymph node metastasis in coeliac ganglia: an important pitfall in clinical practice. *Eur J Nucl Med Mol Imaging*. 2015;42:210–4.
12. Brindle R, Mullan D, Yap BK, Gandhi A. Thyroid incidentalomas discovered on positron emission tomography CT scanning—Malignancy rate and significance of standardised uptake values. *Eur J Surg Oncol*. 2014;40:1528–32.
13. Verburg FA, Krohn T, Heinzel A, Mottaghy FM, Behrendt FF. First evidence of PSMA expression in differentiated thyroid cancer using ^{68}Ga -PSMA-HBED-CC PET/CT. *Eur J Nucl Med Mol Imaging*. 2015;42:1622–3.
14. Demirci E, Ocak M, Kabasakal L, Decristoforo C, Talat Z, Halaç M, et al. ^{68}Ga -PSMA PET/CT imaging of metastatic clear cell renal cell carcinoma. *Eur J Nucl Med Mol Imaging*. 2014;41:1461–2.
15. Chang SS, Reuter VE, Heston WD, Bander NH, Grauer LS, Gaudin PB. Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. *Cancer Res*. 1999;59:3192–8.