J of Nuclear Medicine Technology, first published online March 29, 2018 as doi:10.2967/jnmt.117.203448

Can Ga-68 DOTA Peptides be Potential Radiotracers for PET Imaging of Spleen?

Ismet Sarikaya[1], Abdelhamid H. Elgazzar[1], Ali Sarikaya[2], Naheel Alnafisi[3], Saud Alenezi[1]

[1]Kuwait University Faculty of Medicine, Department of Nuclear Medicine, Kuwait

[2]Trakya University Faculty of Medicine, Department of Nuclear Medicine, Edirne, Turkey

[3]Mubarak Al-Kabeer Hospital, Department of Nuclear Medicine, Kuwait

Correspondence Address:

Ismet Sarikaya, MD, ABNM

Assoc. Professor

Department of Nuclear Medicine

Faculty of Medicine, Kuwait University

PO Box 24923

Safat, Kuwait 13110

Phone: (965) 25319592 / 6414

Fax: (965) 25338936

Email: isarikaya99@yahoo.com

ABSTRACT

On radionuclide somatostatin receptor (SSTR) imaging studies spleen shows very high uptake which is a physiological finding. Reducing intensity of the image settings helps to better assess the distribution of radiotracer in the spleen. In our routine studies we incidentally recognized that Gallium-68 (Ga-68) DOTANOC positron emission tomography (PET) provides higher resolution splenic images as compared to In-111 Octreotide single photon emission computed tomography (SPECT). Autoradiography and immunohistochemistry studies have shown that SSTRs are mainly located in the red pulp of the spleen. Distribution of Ga-68 DOTANOC in the spleen appears to be correlating with the distribution of red pulp. In this article we will present Ga-68 DOTANOC PET/CT spleen images of our patients.

Key words: Spleen, somatostatin receptor, red pulp, Ga-68 DOTANOC, PET/CT

INTRODUCTION

Somatostatin receptor (SSTR) imaging with radiolabeled SST analogs have been used since late 1980s. It is mainly used for the detection, localization, staging and in the follow-up of neuroendocrine tumors (NETs). In early studies Iodine-123 (I-123) Tyr-3-octreotide was used which was later replaced by Indium-111 (In-111) pentetreotide (Octreotide scintigraphy, OctreoScan). Currently, there are new Gallium-68 (Ga-68) labeled SST analogs for positron emission tomography (PET) imaging (1). Conventional SSTR imaging with In-111 pentetreotide is still widely used in the detection of NETs, but new Ga-68 labeled PET radiotracers (Ga-68 DOTATATE, Ga-68 DOTATOC, and Ga-68 DOTANOC) have been increasingly used and replacing conventional SSTR imaging in many centers due better properties of both PET cameras and radiotracers over In-111 pentetreotide and gamma cameras with single photon emission computed tomography (SPECT) imaging. As compared to In-111 pentetreotide imaging, PET scan with Ga-68 DOTA peptides detects more lesions, shows higher uptake in the lesions and provides shorter time of acquisition and lower radiation exposure (2,3).

High splenic uptake on radionuclide SSTR imaging studies is a physiological finding. Because we incidentally recognized that there is higher resolution splenic images with Ga-68 DOTANOC PET/CT as compared to In-111 Octreotide, we decided to present spleen images of our patients in this article.

MATERIAL AND METHODS

Ga-68 DOTANOC PET/CT images were obtained in 7 patients with suspicious or biopsy proven NETs. Radiolabelling was carried out at another institute (Kuwait Cancer Control Center). Images were obtained at Philips Time of Flight PET/CT camera. PET images were obtained 60 min following intravenous injection of 111-185 MBq (3-5 mCi) Ga-68 DOTANOC. Prior to PET image acquisition, a low dose CT was obtained for attenuation correction and anatomic localization purposes. PET acquisition was 3 min/bed from skull base to mid thighs. PET images were corrected for attenuation on the basis of the CT data and reconstructed using a standard iterative algorithm and reformatted into transaxial, coronal and sagittal views. Maximum intensity projection (MIP) images were also generated. Both attenuation corrected (AC) and uncorrected (non-AC) PET images as well as PET/CT fusion images were visually evaluated. Due to intense uptake in the spleen, intensity of the image settings were reduced to better assess distribution of activity in the splenic parenchyma.

RESULTS

Five patients were male (ages 16, 28, 41, 55, and 62 years) and 2 were female (ages 48 and 73 years). Figure 1 shows normal distribution of Ga-68 DOTANOC. Figure 2 shows basic splenic anatomy. Figures 3 shows Ga-68 DOTANOC PET/CT images of the spleen in our 3 patients. Figure 4 shows In-111 pentetreotide images for comparison with Ga-68 DOTANOC images. On Ga-68 DOTANOC PET/CT images spleen shows high uptake with slightly heterogeneous distribution of activity in the parenchyma. Areas showing more prominent uptake in the parenchyma and subcapsular region is probably due to red pulp as it correlates with the distribution of the red pulp. Small areas showing less uptake and located more centrally and in hilar region is likely representing vascular structures and white pulp.

SUVmax values of the spleen and waiting period between Ga-68 DOTANOC injection time and acquisition start time were 41.3/60 min, 41.4/95 min, 58.8/76 min, 62.1/80 min, 67.7/93 min, 69/129 min, and 70.4/109 min in our patients.

DISCUSSION

The spleen has 2 main compartments, the red pulp and the white pulp (Fig. 1). The red pulp is a blood filter that removes foreign materials and damaged and aged red blood cells (RBCs) from the circulation. It is also a storage site for iron, RBCs, and platelets. White pulp surrounds the central arterioles and is composed of periarteriolar lymphoid sheath, the follicles, and the marginal zone. Immune responses to blood-borne antigens occurs in the white pulp (4).

Autoradiography and immunohistochemistry studies have demonstrated that SSTRs are mainly located in the red pulp of the spleen (5-7). Reubi et al. reported that red pulp contains diffusely distributed SSTRs (7). The most abundant SSTR subtype in the spleen was SSTR2 (79.7 %) followed by SSTR1(19.6 %), SSTR4 (0.6%), SSTR3 (0.1%) and SSTR5 (0.0%) (8). Quantitative reverse transcription polymerase chain reaction also showed a significantly higher expression of SST2A mRNA in the spleen (9). Fluorescence immunocytochemistry revealed the presence of SST-positive cells in clusters inside the white pulp and more dispersed within the red pulp of the spleen of both the rat and the chicken (10). Following SST administration there was a marked constriction of the splenic vascular bed with 50% decrease in blood flow which was suggested that this effect of SST was due to a direct action on vascular receptor sites (11). Given high amount of SSTRs in the spleen, it is expected to locate SSTRs also on other sites in red pulp in addition to vascular structures.

Ga-68 DOTANOC PET/CT images provide high quality images of the spleen. The distribution of Ga-68 DOTANOC appears to be correlating with the distribution of red pulp of the spleen. Given excellent splenic images, SSTR PET/CT imaging with Ga-68 labeled DOTANOC or other DOTA peptides may be an alternative to standard radionuclide splenic imaging studies with Tc-99m heat damaged RBCs (selective spleen scintigraphy) or Tc-99m sulfur colloid (Tc-

99m SC). Although standard radionuclide splenic imaging studies are the procedure of choice to image spleen, they have certain limitations. Tc-99m heat damaged RBC study is laborious, time consuming, and requires strict sterile technique (12). Insufficient or excessive damage to RBCs is not uncommon and can cause suboptimal study. Colloid scan with Tc-99m SC is less sensitive than selective spleen imaging in the identification of small splenic tissues (13). High hepatic uptake in colloid scan can mask the visualization of adjacent small splenic tissues. PET imaging of spleen with Ga-68 DOTA peptides not only provides higher quality images than selective spleen SPECT imaging but is also quicker and easier to perform. Radiation dose to spleen also appears to be lower with Ga-68 DOTANOC PET imaging (without including CT) than with Tc-99m heat damaged RBC scintigraphy which is 0.0725 mGy/MBq (0.269 rad/mCi) versus 0.56 mGy/MBq (2.1 rad/mCi), respectively (14,15). However, the main limitations of PET/CT imaging of spleen with Ga-68 DOTA peptides are the high cost of this study and also limited availability. Currently, PET/CT cameras are widely available, but preparation of these radiotracers require costly Ga-68 generator, and radiolabeling synthesis unit.

CONCLUSION

SSTR imaging with PET radiotracers provide high resolution splenic images and we expect that it can be an alternative to standard radionuclide splenic imaging studies to assess morphologic abnormalities of the spleen and detect splenosis and accessory spleen. However, the main limitations of PET/CT imaging of spleen with Ga-68 DOTA peptides are the high cost and limited availability.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Becker W, Marienhagen J, Scheubel R, et al. Octreotide scintigraphy localizes somatostatin receptor-positive islet cellcarcinomas. Eur J Nucl Med 1991;18:924-927.
2. Kowalski J, Henze M, Schuhmacher J, Maecke HR, Hofmann M, Haberkorn U. Evaluation of positron emission tomography imaging using [68Ga]-DOTA-D-Phe1-Tyr3-octreotide in comparison to [111In]-DTPAOC SPECT. First results in patients with neuroendocrine tumors. Mol Imaging Biol 2003;5:42–48.
3. Buchmann I, Henze M, Engelbrecht S, et al.Comparison of 68Ga-DOTATOC PET and 111In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. Eur J Nucl Med Mol Imaging 2007;34:1617–1626.
4. Cesta MF. Normal structure, function, and histology of the spleen. Toxicol Pathol 2006;34:455-465.
5. Reubi JC, Waser B, Horisberger U, et al. In vitro autoradiographic and in vivo scintigraphic localization of somatostatin receptors in human lymphatic tissue. Blood 1993;82:2143-2151.
6. Melis M, Kaemmerer D, de Swart J, et al. Localization of Radiolabeled Somatostatin Analogs in the Spleen. ClinNucl Med 2016;41:e111-114.
7. Reubi JC, Horisberger U, Kappeler A, Laissue JA. Localization of receptors for vasoactive intestinal peptide, somatostatin, and substance P in distinct compartments of human lymphoid organs. Blood 1998;92:191-197.
8. Boy C, Heusner TA, Poeppel TD, et al. 68Ga-DOTATOC PET/CT and somatostatin receptor (sst1-sst5) expression in normal human tissue: correlation of sst2 mRNA and SUVmax. Eur J Nucl Med Mol Imaging 2011;38:1224-1236.

9. Ferone D, Pivonello R, Kwekkeboom DJ, et al. Immunohistochemical localization and quantitative expression of somatostatin receptors in normal human spleen and thymus: Implications for the in vivo visualization during somatostatin receptor scintigraphy. J Endocrinol Invest 2012;35:528-534.

10. Aguila MC, Dees WL, Haensly WE, McCann SM. Evidence that somatostatin is localized and synthesized in lymphoid organs. ProcNatlAcadSci U S A. 1991;88:11485-9.

11. Samnegård H, Tydén G, Thulin L, Friman L, Udén R. Effect of somatostatin on regional splanchnic blood flows in man. Angiographic studies. Acta Chir Cand Suppl 1980;500:71-73.

12. MacDonald A, Burrell S. Infrequently performed studies in nuclear medicine:Part 1. J Nucl Med Technol 2008;36:132-143.

13. Massey MD, Stevens JS. Residual spleen found on denatured red blood cell scan following negative colloid scans. J Nucl Med 1991;32:2286-2287.

14. Balon HR, Brown TL, Goldsmith SJ, et al. Society of Nuclear Medicine. The SNM practice guideline for somatostatin receptor scintigraphy 2.0. J Nucl Med Technol 2011;39:317-324.

15. Pettinato C, Sarnelli A, Di Donna M, et al. 68Ga-DOTANOC: biodistribution and dosimetry in patients affected by neuroendocrine tumors. Eur J Nucl Med Mol Imaging 2008;35:72–79.

FIGURE LEGEND

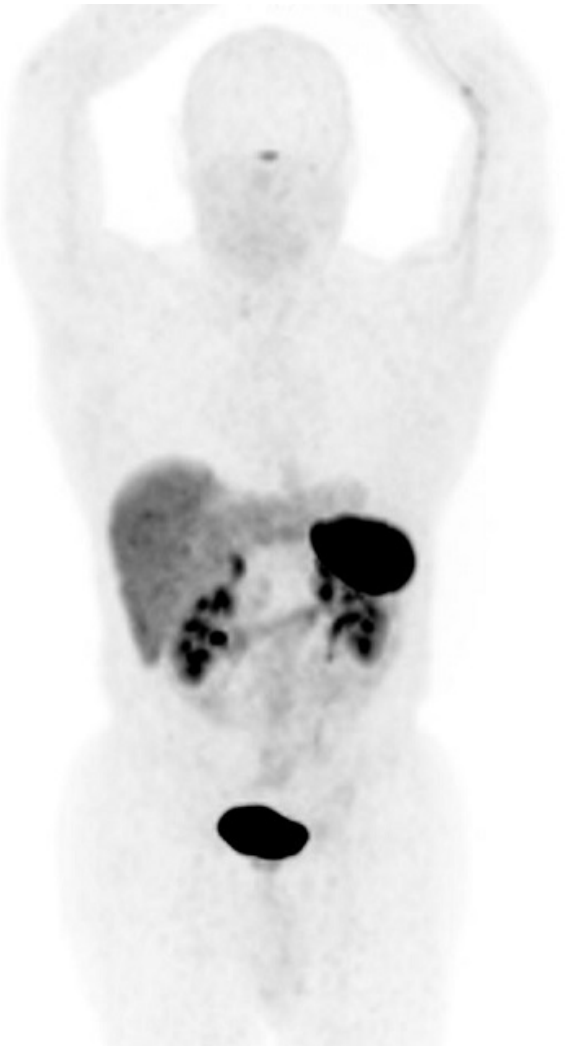

FIGURE 1. Ga-68 DOTANOC whole body PET maximum intensity projection (MIP) image demonstrates normal distribution of activity in the spleen, liver, pituitary gland, adrenal glands, pancreatic head and bowel with excreted activity in the kidneys and bladder.

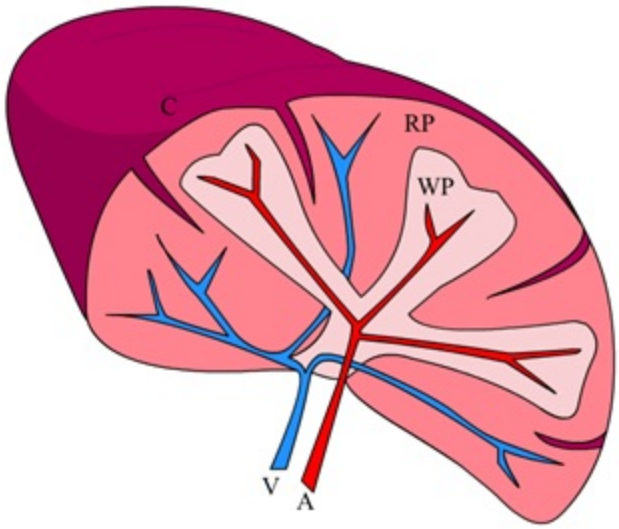

FIGURE 2. Basic anatomy of the spleen: red pulp (RP), white pulp (WP), vein (V), artery (A), and splenic capsule (C).

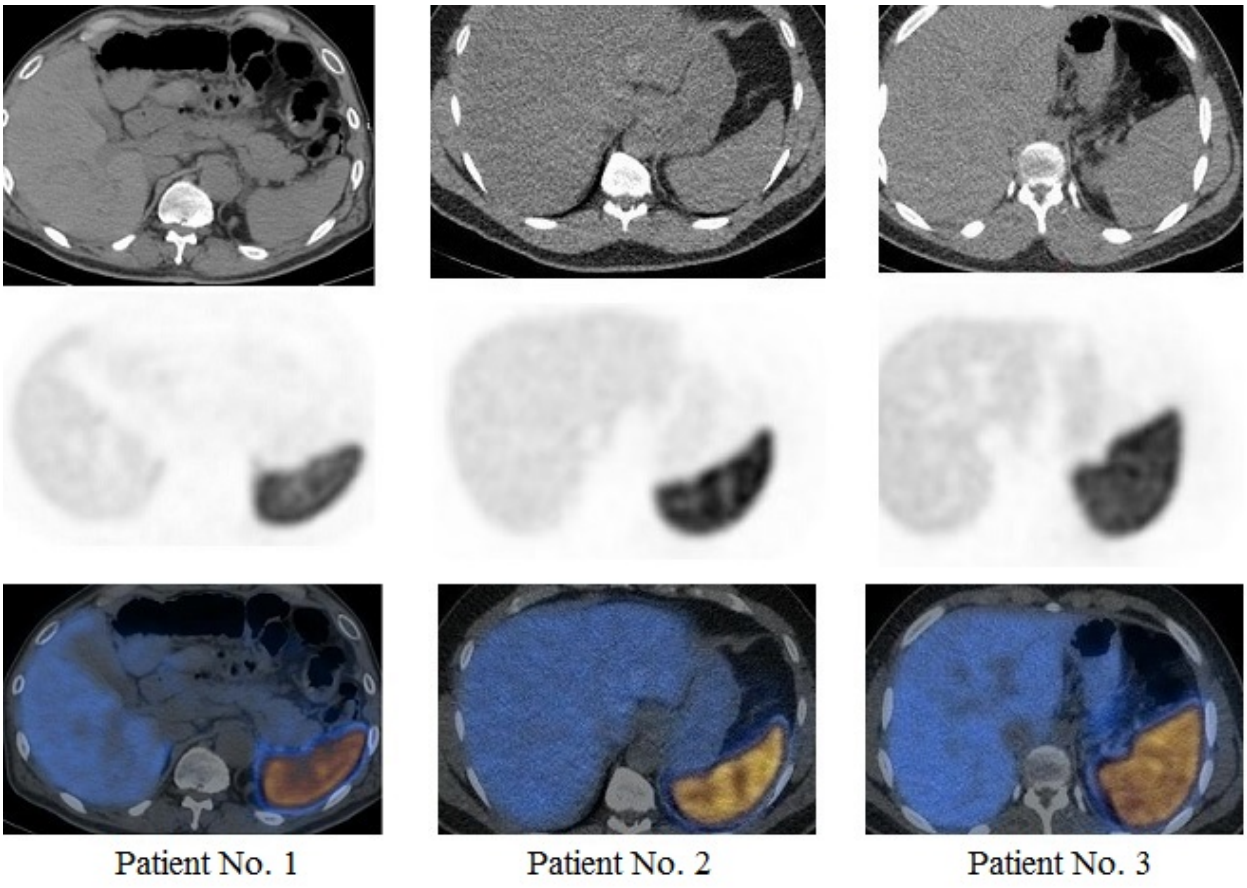

FIGURE 3. Ga-68 DOTANOC selected transaxial CT, PET, and PET/CT fusion images of 3 patients. PET images demonstrate physiological high uptake in the spleen with slight heterogeneous distribution of activity. Slightly more prominent uptake in the periphery of the spleen and focally throughout the splenic parenchyma is likely from subcapsular and parenchymal red pulp. Areas showing less degree of uptake more centrally and in hilar region are likely from splenic vascular structures or white pulp.

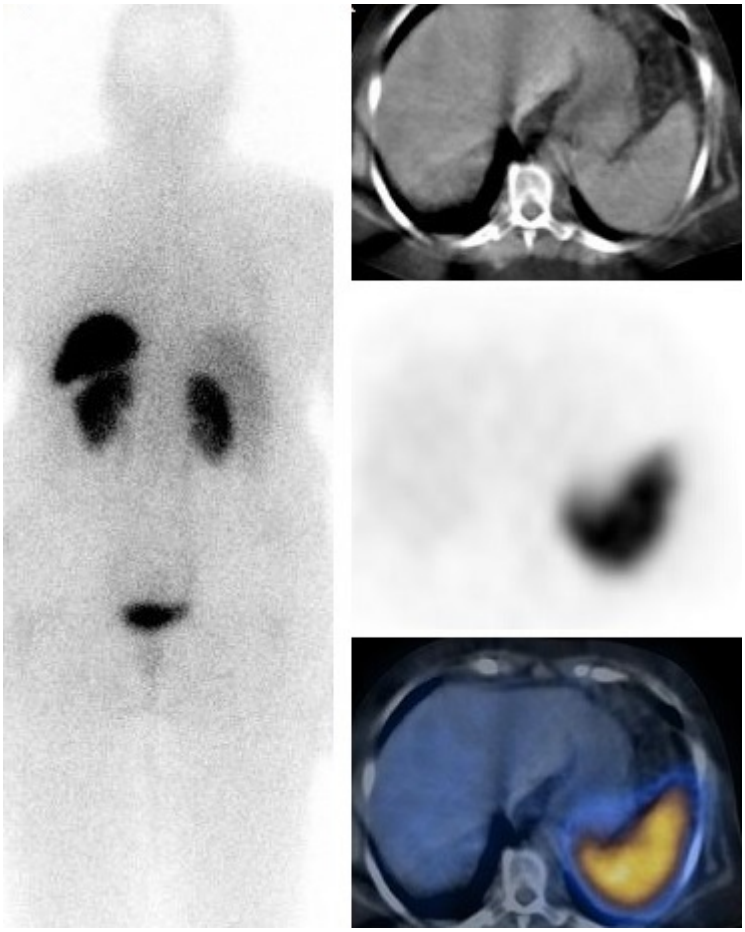

FIGURE 4. In-111 pentetreotide posterior whole body, and selected transaxial CT, SPECT, and SPECT/CT fusion and images. Note the high physiological uptake in the spleen with poor image resolution as compared to higher resolution images with Ga-68 DOTANOC.