Bone and Calcified Soft Tissue Metastases of Medullary Thyroid Carcinoma Better Characterized on ^{18}F -Fluoride PET/CT than on ^{68}Ga -Dotatate PET/CT

Paulo Schiavom Duarte¹ · Luciana Audi de Castroneves² · Heitor Naoki Sado¹ · Marcelo Tatit Sapienza¹ · Ana Amélia Fialho de Oliveira Hoff² · Carlos Alberto Buchpiguel¹

Received: 1 March 2018 / Revised: 6 May 2018 / Accepted: 9 May 2018 / Published online: 4 June 2018

© Korean Society of Nuclear Medicine 2018

Abstract

Herein, we report a case of a 19-year-old man with multiple endocrine neoplasia type 2B (MEN2B) and medullary thyroid carcinoma (MTC) diagnosed when he was 12 years of age. The patient had previously undergone total thyroidectomy, cervical radiotherapy, and chemotherapy. He progressed with known bone, pulmonary, and lymph node metastases and was scanned with ^{18}F -fluoride (^{18}F -NaF) and ^{68}Ga -dotatate whole-body positron emission tomography/computed tomography (PET/CT) for metastatic disease monitoring. We found that the MTC bone metastases and soft tissue calcified metastases were better characterized on ^{18}F -NaF PET/CT than on ^{68}Ga -dotatate PET/CT. This case illustrates that the ^{18}F -NaF PET/CT could be helpful not only to the detection of bone metastases but also to the detection of calcified soft tissue metastases in patients with MTC.

Keywords Medullary thyroid carcinoma · Gallium-68 · ^{68}Ga · ^{18}F · ^{18}F -NaF · PET/CT

Introduction

Medullary thyroid carcinoma (MTC) is a rare neuroendocrine malignancy originating from the thyroid parafollicular C cells and, according to recent SEER (Surveillance, Epidemiology and End Results) data, accounts only for 1–2% of thyroid cancers in the USA [1]. The C cells secrete carcinoembryonic antigen (CEA) and calcitonin [2, 3] that are valuable tumor markers in patients with MTC [4]. Their serum concentrations are directly related to the C cell mass and simultaneous elevations of both in patients with MTC indicate disease progression [4]. In a study evaluating patients prior to thyroidectomy for MTC [5], when the baseline serum calcitonin level was less than 500 pg/mL, no distant metastases were detected. In

the postoperative follow-up, if the serum calcitonin level exceeds 150 pg/mL, patients should be evaluated by imaging procedures, including neck ultrasonography (US), chest computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), or three-phase contrast-enhanced CT of the liver, bone scintigraphy, and MRI of the pelvis and axial skeleton [1]. Previous studies found that in patients with MTC, neck US is the most sensitive tool to detect cervical lymph node metastases [6], CT is superior to any other technique to detect lung lesions [7], and MRI is the most sensitive imaging modality for detection of hepatic and bone metastatic disease [8, 9]. However, bone scintigraphy and whole-body MRI (WB-MRI) were complementary for detection of bone metastases since WB-MRI may not always detect peripheral lesions located in the ribs, skull, and sternum [6, 10, 11]. Therefore, imaging MTC would consist in the combination of the aforementioned procedures [6].

Regarding positron emission tomography/computed tomography (PET/CT) scan, only one study comparing ^{18}F -DOPA, ^{18}F -FDG, and somatostatin receptor PET/CT in recurrent MTC is available [12]. This study showed the superior diagnostic accuracy of ^{18}F -DOPA compared over other PET radiopharmaceuticals in this indication [12]. However, somatostatin receptor PET/CT may have an additional role as

✉ Paulo Schiavom Duarte
psduarte@hotmail.com

¹ Division of Nuclear Medicine, São Paulo Cancer Institute (ICESP), Av. Dr. Arnaldo, 251, 4° SS, Cerqueira César, São Paulo, SP 01246-000, Brazil

² Division of Endocrinology, São Paulo Cancer Institute (ICESP), São Paulo, Brazil

this method could be useful in pre-selecting metastatic MTC patients for therapy with cold or radiolabelled somatostatin analogues [13]. Nevertheless, the international guidelines do not recommend the use of any PET/CT tracers for restaging MTC with biochemical failure. The 2012 European Thyroid Association Guidelines for metastatic MTC recommend only the use of bone scintigraphy while the use of PET with ^{18}F -DOPA or ^{18}F -FDG is not advocated for its cost and low sensitivity, respectively [14]. In 2015, The Revised American Thyroid Association guidelines for the management of

medullary thyroid carcinoma corroborated that neither ^{18}F -FDG-PET/CT nor ^{18}F -DOPA-PET/CT is recommended to detect the presence of distant metastases [1]. However, there are some objections to these guidelines and the European Association of Nuclear Medicine refuses to endorse some of the recommendations since they marginalize the utility of the nuclear medicine procedures in the management of the patients with MTC [15].

^{18}F -Fluoride (^{18}F -NaF) is a positron emission tracer used to evaluate benign and malignant bone diseases, mainly bone

Fig. 1 ^{18}F -Fluoride (a) and ^{68}Ga -dotatate (b) PET coronal maximum intensity projection (MIP) images demonstrated uptake of both radiopharmaceuticals in multiple bone metastases (arrowheads). However, the metastases were better depicted on ^{18}F -fluoride PET/CT

metastatic diseases. In the last years, there has been an increased clinical interest in the use of ^{18}F -NaF for bone disease assessment [16]. Reasons for this resurgence include the improved sensitivity of ^{18}F -NaF PET/CT compared with technetium-based conventional bone scans [17], the quantitative potential of ^{18}F -NaF PET/CT [18], and the periodic international shortages of Tc-99m needed for conventional bone scintigraphy [19]. Although the ^{18}F -NaF PET/CT scan has been evaluated in the assessment of metastatic bone disease in a variety of neoplastic disease, principally in prostate and breast cancer [20], its use in MTC has been barely evaluated. In the herein reported case, we described the potential of the ^{18}F -NaF to detect not only bone metastatic disease but also calcified soft tissue disease in a patient with MTC.

Case Report

A 19-year-old man had multiple endocrine neoplasia type 2B (MEN2B) and MTC diagnosed when he was 12 years old. He was submitted to total thyroidectomy, cervical radiotherapy, and systemic chemotherapy with irinotecan and thalidomide. However, he progressed with known bone, pulmonary, and lymph node metastases and was started on vandetanib, a kinase inhibitor of the vascular endothelial growth factor receptor (VEGFR), the epidermal growth factor receptor (EGFR), and the RET-tyrosine kinase. He was scanned with ^{18}F -fluoride (^{18}F -NaF) and ^{68}Ga -dotatate whole-body positron emission tomography/computed tomography (PET/CT) for metastatic disease monitoring and also underwent a CT scan of the

Fig. 2 Coronal ^{18}F -NaF PET image (a) demonstrated a heterogeneous uptake in the lungs with widespread focal areas with more conspicuous uptake and moderate focal uptake in the mediastinum (arrowhead). Coronal ^{68}Ga -dotatate PET images (b) demonstrated faint heterogeneous uptake in the lungs and a focal mild radiotracer uptake in the mediastinum (arrowhead). Focal uptake in the humeri is also observed (double arrowheads), more evident in the ^{18}F -NaF PET image. The chest CT images in lung (c) and mediastinal (d) windows demonstrated multiple nodules widespread in both lungs, some of them calcified and calcified mediastinal lymph nodes (arrowhead)

neck, chest, and abdominal regions. At the time of the scans, the serum calcitonin and CEA levels were 59,979.0 pg/mL and 650.1 ng/mL, respectively.

^{18}F -NaF and ^{68}Ga -dotatate PET/CT studies performed 40 days apart (^{68}Ga -dotatate first) demonstrated uptake of

both radiopharmaceuticals in bone and calcified soft tissues metastases. However, the metastases were better depicted on ^{18}F -NaF (Figs. 1, 2, and 3).

When the ^{18}F -NaF regions of uptake were compared with CT imaging of the chest and abdominal regions, it

Fig. 3 Coronal ^{18}F -NaF PET image (a) demonstrated a heterogeneous uptake in lungs and areas with moderate focal uptake in the upper mediastinum and abdominal regions (arrowheads). Coronal ^{68}Ga -dotatate PET images (b) demonstrated faint heterogeneous uptake in lungs and focal mild radiotracer uptake in the mediastinum (arrowhead). The abdominal lesions were not depicted on the ^{68}Ga -dotatate PET images. It is also observed focal uptake in the right parietal region (double arrowheads), more evident in the ^{18}F -NaF PET image. The chest (c) and abdomen (d) CT demonstrated multiple calcified nodules widespread in both lungs and calcified mediastinal and abdominal lymph nodes (arrowheads)

was possible to realize that most of the calcified soft tissue metastatic lesions presented ^{18}F -NaF uptake suggesting the high sensitivity of the method in the presented case (Figs. 2 and 3). It was also noted that both PET/CT studies were equally capable to detect a cerebellum calcified metastasis (Fig. 4).

Discussion

Conventional bone scintigraphy using $^{99\text{m}}\text{Tc}$ -methylene diphosphonate ($^{99\text{m}}\text{Tc}$ -MDP) is one of the imaging techniques used to detect MTC metastatic disease in the skeleton. Its use in the management of MTC has been recommended by the guidelines of the American Thyroid Association [1, 14]. However, in the last years, PET/CT scanners have become increasingly available, and this has increased the interest in using ^{18}F -NaF PET/CT for skeletal imaging.

As previously said, ^{18}F -NaF is a positron emission tracer used to evaluate benign and malignant bone diseases, mainly, bone metastatic diseases. Although the ^{18}F -NaF PET/CT scan has been evaluated in the assessment of metastatic disease in a variety of neoplastic disease [20], its use in MTC has been barely described. Since ^{18}F -NaF PET/CT has systematically been shown to present higher accuracy in comparison with conventional bone scintigraphy using $^{99\text{m}}\text{Tc}$ -MDP [16], its comparison with other imaging techniques in the evaluation of bone metastases in patients with MTC should be an important task. However, this comparison is very rare in the scientific literature. For example, comparison of ^{18}F -NaF and ^{68}Ga -dotatate uptake in bone metastatic lesions of MTC has been described in only one report [21]. This report described a single case of a patient for whom both methods were complementary in the detection of bone lesions and the comparison of the ^{18}F -NaF with other PET/CT tracers as well as with bone scintigraphy in the detection of skeletal metastases in patients with MTC has not been described. The lack of scientific studies on this topic should be due to the low prevalence of the disease [1] and the recent renewed interest of the use of the ^{18}F -NaF in the clinical practice [16]. Therefore, series of cases

or case reports comparing ^{18}F -NaF with other imaging methods in the assessment of bone metastases in patients with MTC should be helpful to understand the role of this technology in clinical practice.

In addition, beyond the detection of bone metastases, $^{99\text{m}}\text{Tc}$ -MDP and ^{18}F -NaF can also detect calcified soft tissue metastases [22, 23]. Specifically in MTC cases, one report has described the capability of $^{99\text{m}}\text{Tc}$ -MDP bone scintigraphy to detect calcified hepatic metastases [24] and there is also one report on the ^{18}F -NaF uptake in lymph nodal and hepatic MTC calcified metastatic lesions [25]. However, at the time being, there is no report comparing the ^{18}F -NaF detection of calcified soft tissue MTC metastases with other diagnostic imaging methods. This comparison would be interesting, since calcification is a frequent finding in soft tissue metastases of MTC [26] and the ^{18}F -NaF PET/CT could be useful in the detection of these metastases.

In this aspect, the herein reported case illustrates the potential of the ^{18}F -NaF to detect not only bone metastatic disease but also calcified soft tissue disease in a patient with MTC. In this case, the ^{18}F -NaF was superior to the ^{68}Ga -dotatate in the detection of metastatic sites in bone and calcified soft tissue metastases and depicted most of the soft tissue calcified lesions detected on the CT. The reason for this superiority of the ^{18}F -NaF could be a low expression of somatostatin receptors (SSTR) in some of the metastatic sites since this expression is variable [27]. Indeed, the sensitivity of ^{68}Ga -somatostatin analogue PET/CT in the detection of recurrence in patients with MTC has been reported to be limited and even in the same patient some metastatic sites present uptake of the radiopharmaceutical, while others do not [12].

It is also interesting to note that the ^{18}F -NaF was capable to detect brain calcified metastases. This is particularly important since this is a region not routinely scanned in the algorithm recommended by the guidelines of the American Thyroid Association [1, 14]. Therefore, metastases in this region, although not common, could be missed using the current guidelines, and the use of ^{18}F -NaF PET/CT instead of conventional bone scintigraphy could be an opportunity to detect these metastases.

Fig. 4 ^{18}F -NaF PET (a), ^{68}Ga -dotatate PET (b), and CT transaxial images (c) at the level of the cerebellum demonstrated focal uptake of both radiopharmaceuticals at a calcified lesion in the left cerebellar hemisphere (arrowheads)

In conclusion, this case suggests that at least in some situations, the ^{18}F -NaF PET/CT studies could be helpful in the detection of bone as well as calcified soft tissue metastases when in comparison with ^{68}Ga -dotatate PET/CT and conventional CT scan. Nonetheless, further analysis including a greater number of patients is required to confirm these findings.

Compliance with Ethical Standards

Conflict of Interest Paulo Schiavom Duarte, Luciana Audi de Castroneves, Heitor Naoki Sado, Marcelo Tatit Sapienza, Ana Amélia Fialho de Oliveira Hoff, and Carlos Alberto Buchpiguel declare no conflict of interest.

Ethical Approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The institutional review board of our institute approved this case report, and the requirement to obtain informed consent was waived.

References

- Wells SA Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid*. 2015;25:567–610.
- Abe K, Adachi I, Miyakawa S, et al. Production of calcitonin, adrenocorticotrophic hormone, and beta-melanocyte-stimulating hormone in tumors derived from amine precursor uptake and decarboxylation cells. *Cancer Res*. 1977;37:4190–4.
- Ishikawa N, Hamada S. Association of medullary carcinoma of the thyroid with carcinoembryonic antigen. *Br J Cancer*. 1976;34:111–5.
- Mendelsohn G, Wells SA Jr, Baylin SB. Relationship of tissue carcinoembryonic antigen and calcitonin to tumor virulence in medullary thyroid carcinoma. An immunohistochemical study in early, localized, and virulent disseminated stages of disease. *Cancer*. 1984;54:657–62.
- Machens A, Dralle H. Biomarker-based risk stratification for previously untreated medullary thyroid cancer. *J Clin Endocrinol Metab*. 2010;95:2655–63.
- Giraudet AL, Vanel D, Lebouilleux S, et al. Imaging medullary thyroid carcinoma with persistent elevated calcitonin levels. *J Clin Endocrinol Metab*. 2007;92:4185–90.
- Szakall S Jr, Esik O, Bajzik G, et al. ^{18}F -FDG PET detection of lymph node metastases in medullary thyroid carcinoma. *J Nucl Med*. 2002;43:66–71.
- Dromain C, de BT, Lumbroso J, et al. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. *J Clin Oncol*. 2005;23:70–8.
- Mirallie E, Vuillez JP, Bardet S, et al. High frequency of bone/bone marrow involvement in advanced medullary thyroid cancer. *J Clin Endocrinol Metab*. 2005;90:779–88.
- Altehoefer C, Ghanem N, Hogerle S, et al. Comparative detectability of bone metastases and impact on therapy of magnetic resonance imaging and bone scintigraphy in patients with breast cancer. *Eur J Radiol*. 2001;40:16–23.
- Ghanem N, Uhl M, Brink I, et al. Diagnostic value of MRI in comparison to scintigraphy, PET, MS-CT and PET/CT for the detection of metastases of bone. *Eur J Radiol*. 2005;55:41–55.
- Treglia G, Castaldi P, Villani MF, et al. Comparison of ^{18}F -DOPA, ^{18}F -FDG and ^{68}Ga -somatostatin analogue PET/CT in patients with recurrent medullary thyroid carcinoma. *Eur J Nucl Med Mol Imaging*. 2012;39:569–80.
- Salavati A, Puranik A, Kulkarni HR, et al. Peptide receptor radionuclide therapy (PRRT) of medullary and nonmedullary thyroid cancer using radiolabeled somatostatin analogues. *Semin Nucl Med*. 2016;46:215–24.
- Schlumberger M, Bastholt L, Dralle H, et al. European thyroid association guidelines for metastatic medullary thyroid cancer. *Eur Thyroid J*. 2012;21:1–14.
- Treglia G, Aktolun C, Chiti A, et al. The 2015 revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma: the “evidence-based” refusal to endorse them by EANM due to the “not evidence-based” marginalization of the role of nuclear medicine. *Eur J Nucl Med Mol Imaging*. 2016;43:1486–90.
- Grant FD, Fahey FH, Packard AB, et al. Skeletal PET with ^{18}F -fluoride: applying new technology to an old tracer. *J Nucl Med*. 2008;49:68–78.
- Even-Sapir E, Metser U, Mishani E, et al. The detection of bone metastases in patients with high-risk prostate cancer: $^{99\text{m}}\text{Tc}$ -MDP planar bone scintigraphy, single- and multi-field-of-view SPECT, ^{18}F -fluoride PET, and ^{18}F -fluoride PET/CT. *J Nucl Med*. 2006;47:287–97.
- Doot RK, Muzi M, Peterson LM, et al. Kinetic analysis of ^{18}F -fluoride PET images of breast cancer bone metastases. *J Nucl Med*. 2010;51:521–7.
- Perkins A, Hilson A, Hall J. Global shortage of medical isotopes threatens nuclear medicine services. *BMJ*. 2008;337:a1577.
- Kulshrestha RK, Vinjamuri S, England A, et al. The role of ^{18}F -sodium fluoride PET/CT bone scans in the diagnosis of metastatic bone disease from breast and prostate cancer. *J Nucl Med Technol*. 2016;44:217–22.
- Basu S, Ranade R, Thapa P. ^{177}Lu -DOTATATE versus ^{177}Lu -EDTMP versus cocktail/sequential therapy in bone-confined painful metastatic disease in medullary carcinoma of the thyroid and neuroendocrine tumour: can semiquantitative comparison of ^{68}Ga -DOTATATE and ^{18}F -fluoride PET-CT aid in personalized treatment decision making in selecting the best therapeutic option? *Nucl Med Commun*. 2016;37:100–2.
- Tokuue K, Furuse M. Usefulness of the $^{99\text{m}}\text{Tc}$ -MDP scan in the detection of calcified liver metastases. *Nuklearmedizin*. 1990;29:231–3.
- Li Y, Tafti BA, Shaba W, et al. Extraosseous uptake of ^{18}F -fluoride in the primary malignancy and cerebral metastasis in a case of non-small-cell lung cancer. *Clin Nucl Med*. 2011;36:609–11.
- Ali I, Johns W, Gupta SM. Visualization of hepatic metastases of medullary thyroid carcinoma on $^{99\text{m}}\text{Tc}$ MDP bone scintigraphy. *Clin Nucl Med*. 2006;31:611–3.
- do Vale RH, Marin JF, Duarte PS, et al. Visualization of lymph nodal and hepatic metastases of medullary thyroid carcinoma on ^{18}F -fluoride PET/CT. *Clin Nucl Med*. 2015;40:895–6.
- Williams ED, Brown CL, Doniach I. Pathological and clinical findings in a series of 67 cases of medullary carcinoma of the thyroid. *J Clin Pathol*. 1966;19:103–13.
- Papotti M, Kumar U, Volante M, et al. Immunohistochemical detection of somatostatin receptor types 1–5 in medullary carcinoma of the thyroid. *Clin Endocrinol*. 2001;54:641–9.