Osteoblastic bone metastases from neuroendocrine tumor (NET) of unknown origin detected by $^{18}$F-fluorocholine PET/CT and its comparison with $^{68}$Ga-DOTATOC PET/CT

Case report and review of the literature

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Abstract

Rationale: Choline (CH) positron emission tomography (PET)/computed tomography (CT) with fluorine 18 ($^{18}$F) CH is increasingly used not only to evaluate patients with biochemically recurrent prostate cancer but also to assess metastatic lesions that are difficult or impossible to identify using more conventional modalities. Our experience with CH PET/CT has shown that it can also be used for many other malignancies.

Presenting concerns: A 71-year-old male with a neuroendocrine tumor (NET) of unknown origin showed osteoblastic bone metastases positive to $^{18}$F-CH PET.

Interventions: Diffuse bone and liver metastases were $^{68}$Ga-DOTATOC PET-positive with only mild uptake on $^{18}$FDG PET/CT. An increased prostate specific antigen (8 µg/L) gave rise to a suspicion of concurrent prostate cancer and the patient underwent $^{18}$F-CH PET/CT which showed diffuse uptake in the bone. A CT-guided bone biopsy confirmed osteoblastic bone metastases from NET.

Outcomes: Given the aggressiveness of the tumor, the patient underwent treatment with temozolomide from July 2015 to December 2015, maintaining stable disease. However, progression was documented in January 2016 and the patient was enrolled onto a phase II peptide receptor radionuclide therapy retreatment trial, which is currently ongoing.

Main lesson: Our study highlights that NETs should be taken into consideration in the differential diagnosis of osteoblastic bone metastases showing $^{18}$F-CH uptake. A prognostic role for this imaging technique can also be hypothesized.

Abbreviations: CH = choline, CT = computed tomography, $^{18}$F = 18 fluorocholine, $^{68}$Ga, 68 gallium, NET = neuroendocrine tumor, PET = positron emission tomography, PRRT = peptide receptor radionuclide therapy.

Keywords: $^{18}$F-CH PET/CT, $^{18}$FDG PET/CT, $^{68}$Ga-PET/CT, neuroendocrine tumor, osteoblastic bone metastases
1. Introduction

Neuroendocrine tumors (NETs) represent a heterogeneous group of relatively rare neoplasms arising from cells of the endocrine system.[1] The incidence of these tumors is low (5.25/100,000/year) but has increased significantly in recent years and prevalence is high (35/100,000/year) given of the long survival of these patients.[2] The medical approach to metastatic disease takes into account the anatomical origin, degree of differentiation, and endocrine function of the tumor, and includes numerous therapeutic options. NETs can be classified as functioning or nonfunctioning according to the presence or not of peptide or hormone secretion. In about 20% to 50% of cases, the primary tumor is of unknown origin, accounting for 2% to 4% of all cancers of unknown primary origin.[3-5]

Tumor grade is determined on the basis of Ki67 proliferation index within the neoplastic cell population; low and medium grade lesions are classified as NETs, whereas high grade lesions are considered to be more aggressive and are classified as neuroendocrine carcinomas.[6] These neoplasms are characterized by an overexpression of somatostatin receptors. Gallium-68Ga-DOTATOC positron emission tomography (PET)/computed tomography (CT) plays a crucial part in the diagnostic and therapeutic management strategies of these tumors.[7,9]

F-fluorodeoxyglucose (FDG) is the most widely used glucose analog for PET imaging studies and is particularly sensitive for tumors exhibiting rapid and aggressive growth.[10] FDG uptake is closely linked to tumor vascularization and hydrocarbon metabolism and, therefore, to its replicating power.[11]

Although radiolabeled choline (CH) PET/CT is widely accepted as a useful tool in prostate cancer staging, several human tumor-derived cell lines of different cancer histologies including breast, colon, prostate, lung, brain, and liver have shown an increased CH metabolism.[12,13] Some authors have also indicated the potential usefulness of 11C-C- and 18 fluor (18F)-labeled CH PET/CT in bronchial NETs. No data are available on NETs of different origin.[14,15]

We present the case of a 71-year-old male with no comorbidities other than essential hypertension who was diagnosed with liver metastases from a NET of unknown origin. A comparison was also performed between [18F]-CH PET/CT findings and 68Ga PET/CT and [18F]FDG PET/CT results. We also performed a brief review of the literature, focusing on solid tumors other than from prostate cancer detected by [18F]-CH PET/CT. Institutional review board approval and informed consent were waived as this was a retrospective case report with no identifying patient information presented.

2. Case presentation

Ethics approval was not necessary for this work due to its design (Case Report). Written informed consent was obtained from our patient for the submission of this manuscript and accompanying images.

A 70-year-old male with no comorbidities other than essential hypertension was diagnosed with liver metastases from a NET of unknown origin in 2004 and came to our institute for a second opinion. Eastern Cooperative Oncology Group performance status was 0. After a careful review of the patient’s medical history, the multidisciplinary medical team recommended a wedge resection of liver segments IV and V, hepatic hilum lymphadenectomy, appendectomy, and cholecystectomy, performed in November of the same year. The histology report revealed liver and lymph node metastases from a well-differentiated NET and chronic mild cholecystitis. No evidence of neoplastic disease was found in the other surgical specimens.

In 2015, a whole body CT scan and 68Ga PET/CT showed systemic recurrence with skeletal and liver involvement. The patient also performed a [18F]FDG-PET/CT which, however, did not show increased metabolic uptake. Given the indolent course of the patient’s disease, the multidisciplinary team decided to start 1st-line therapy with long-acting release (LAR) octreotide at a dose of 30 mg following subcutaneous induction. After the 1st subcutaneous administration of octreotide the patient developed dyspnea and glottis edema which rapidly resolved with corticosteroid and antihistamine therapy. Following reevaluation by the multidisciplinary team, the patient was enrolled onto a phase II trial of peptide receptor radionuclide therapy (PRRT).

From August 2010 to May 2011 he completed 5 cycles of lutetium-DOTATATE-PRRT with a cumulative dose of 720 mCi, obtaining a partial response documented in both morphological and metabolic imaging studies. From August 2014 to April 2015 the patient underwent 1st-line metronomic capécitabine, showing a partial response in the liver lesions but progression in terms of the increased number and extension of bone metastases. These unusual findings were discussed by our institute’s Osteoncology Multidisciplinary Group and a new radionuclide evaluation with both 68Ga PET/CT and [18F]FDG PET/CT was performed. The former showed widespread, intensely 68Ga-avid skeletal disease (standardized uptake value (SUV)max at the left iliac crest: 83) and liver involvement (SUVmax: 47.6) (Fig. 1A). The 18F-FDG PET/CT revealed very mild to mild tracer uptake in a few pelvic and vertebral bone lesions (SUVmax at the left iliac crest: 4.1) (Fig. 1B).

Given the discrepancy between the viscer and skeletal response to 1st-line chemotherapy and the suspicion of the presence of a concurrent prostatic tumor, a [18F]-CH PET/CT was performed. Corresponding [18F]-CH PET/CT images documented mild-to-moderate uptake in a number of axial and appendicular skeletal lesions (SUVmax at the left iliac crest: 7.5) (Fig. 1C). Coregistered CT imaging showed a sclerotic pattern of some prominent lumbosacral and pelvic bony lesions that were positive to 68Ga-DOTATOC.

A CT-guided bone biopsy of an osteoblastic lesion at the left iliac crest positive to both [18F]-CH and 68Ga PET/CT was carried out (Fig. 2). The histology revealed a bone localization from a NET G1 according to the 2010 WHO classification. Immuno-histochemical assays were positive for synaptophysin and negative for prostate specific antigen, chromogranin A, transcription termination factor 1, and caudal type homeobox 2.

The Ki67 proliferation index was 1% (Fig. 3). The patient underwent treatment with temozolomide from July 2015 to December 2015, maintaining stable disease. However, progression was documented in January 2016 and the patient was enrolled onto a phase II PRRT retreatment trial, which is currently ongoing.

3. Discussion

Over the past decade, the advent of new diagnostic tools such as 68Ga-DOTA-peptide PET/CT and the use of novel therapeutic agents have led to an increase of survival of patients with NETs.[16-19] Thus, an identification of easily assessable prognostic parameters is crucial for an accurate evaluation both at baseline and during the course of the disease because an initially indolent tumor may become aggressive. To this purpose, PET/CTs provide a functional evaluation of the whole tumor burden that is not feasible with the commonly used Ki-67 parameter.[16-19] CH PET/CTs
also represent an optimal imaging modality for the assessment of bone metastases from prostate cancer, showing high specificity.\(^{[20]}\)

Beheshti et al evaluated 70 patients with biopsy-proven prostate cancer submitted to \(^{18}\)F-CH PET/CT for either preoperative staging (n = 32) or follow-up evaluation (n = 38). The accuracy of bone metastasis detection was 84\%.\(^{[21]}\)

Comparing \(^{11}\)C-CH PET/CT with MRI in prostate cancer staging, Eschmann et al observed similar high accuracy in the detection of bone metastases for both imaging modalities.\(^{[22]}\)

Radiolabeled CH uptake reflects the increased demands of this precursor for the synthesis of membrane phospholipids in tumor cells with a high proliferation rate.\(^{[11]}\) Based on this, radiolabeled CH was introduced as a PET tracer for brain tumors and prostate cancer in 1970.\(^{[12,15]}\) Numerous case reports and clinical studies have also been published on \(^{18}\)F-CH PET/CT positivity in other solid tumors.\(^{[13,22]}\) In a recent paper by Sollini et al,\(^{[23]}\) 7 patients with biochemical prostate cancer recurrence underwent \(^{18}\)F-CH PET/CT and positive lesions were biopsied. Lung cancer was found in 5 patients, colorectal cancer in 1 patient, and lymph...

Figure 1. A 71-year-old man treated with temozolomide for advanced NET of unknown origin with widespread bone disease, liver metastases, and increased serum PSA (8.0ng/mL). (A) \(^{68}\)Ga-DOTATOC PET/CT axial, sagittal, and maximum intensity projection views show widespread intensely \(^{68}\)Ga-DOTATOC-avid skeletal disease (SUV\(_{\text{max}}\) at the left iliac crest: 83); and liver involvement (SUV\(_{\text{max}}\): 47.6). (B) Corresponding \(^{18}\)F-FDG PET/CT axial and sagittal views showing very mild-to-mild tracer uptake in a few pelvic and vertebral bone lesions (SUV\(_{\text{max}}\) at the left iliac crest: 4.1). (C) Corresponding \(^{18}\)F-FCH PET images document mild-to-moderate \(^{18}\)F-FCH uptake in a number of axial and appendicular skeletal lesions (SUV\(_{\text{max}}\) at the left iliac crest: 7.3). \(^{18}\)F-FCH coregistered low-dose CT shows the sclerotic pattern of some prominent lumbosacral and pelvic bone lesions, all positive to \(^{68}\)Ga-DOTATOC. CT = computed tomography, \(^{18}\)F = \(^{18}\)fluoro, FCH = fluorocholine, \(^{68}\)Ga = \(^{68}\)gallium, NET = neuroendocrine tumor, PET = positron emission tomography, PSA = prostate specific antigen, SUV = standardized uptake value.

Figure 2. Computed tomography (CT)-guided bone biopsy: CT-guided needle biopsy of the 22-mm oval-shaped sclerotic bone lesion located at the left iliac crest, close to the sacroiliac synchondrosis.

Figure 3. Bone biopsy histology report: osteoblastic bone metastases from NET G1 according to WHO classification, synaptophysin-positive (A) and negative for PSA, chromogranin A, TTF1, and CDX2. Ki67 was 1%. Mitosis and tumor cell necrosis not detected (B, C). CDX2 = caudal type homeobox 2, NET = neuroendocrine tumor, PSA = prostate specific antigen, TTF1 = transcription termination factor 1, WHO = World Health Organization.
node metastases from melanoma in 1 patient. In a case report by Vadrucci et al., a 79-year-old patient with prostate cancer showed 18F-Ch-PET/CT uptake in a left pelvic lymph node and the right breast, the latter histologically diagnosed as infiltrating ductal carcinoma. Picardo et al. observed that a lymph node metastasis in the left laterocervical region of a patient with differentiated thyroid cancer was negative to 18F-FDG PET/CT but correctly diagnosed by 18F-Ch-PET/CT, indicating that F-Ch PET/CT may provide more accurate information than 18F-FDG PET/CT on aggressive cancers. Calabria et al. reported that benign tumors such as thymoma, adrenal adenoma, sarcoidosis, and meningioma can also be detected by 18F-Ch-PET/CT, suggesting that these diseases should be evaluated by a nuclear physician because of the intrinsic pharmacologic property of the tracer. How Kit et al. reported that there were no apparent differences that could help to distinguish prostate cancer recurrence from other solid tumors in a large series of patients with increasing prostate specific antigen levels who were positive to 18F-FDG and 18F-Ch-PET/CT. The authors concluded that when more than 1 diagnosis is a possibility, lesions should be biopsied.

To the best of our knowledge, this is the first study to document NET-derived osteoblastic bone metastases detected by 18F-Ch-PET/CT. The case described highlights some important points. First, it confirms that osteoblastic bone lesion positivity to 18F-Ch-PET/CT is not only specific for metastases from prostate cancer but also for other solid neoplasms such as NETs. Furthermore, in our patient the shift from negative to positive in 18FDG PET/CT imaging was suggestive of a transformation from indolent to more aggressive disease not detected by bone biopsy and less responsive to treatment.

CH is a precursor of phosphatidylcholine which is a membrane lipid component. The synthesis of lipid membrane and DNA takes place during cell proliferation. Ablation CH metabolism characterized by increased phosphocholine and total CH-containing compounds reflects the complex interactions between cellular metabolism and proliferative signaling. An increased CH metabolism related to a greater activity of choline kinase-α has been reported in various human malignancies, suggesting a prognostic role of choline kinase-α overexpression. In our patient, Ga PET/CT showed a high expression of somatostatin receptors that correlated with a more indolent clinical course, whereas 18F-FDG PET/CT uptake indicated more aggressive disease. Note, 18F-Ch-PET/CT was more sensitive than 18F-FDG PET/CT in several of the bone lesions, reflecting the capacity of the former scan to detect early changes in the metabolic behavior of the tumor. This could be useful for tumors in which prognostic factors are lacking.

4. Conclusions

18F-Ch-PET/CT interpretation can be challenging because of the possibility of tracer uptake from other solid malignancies and benign lesions. NETs should also be included in the differential diagnosis of osteoblastic bone metastases showing 18F-Ch-PET/CT uptake. Our findings suggest a potential prognostic role of 18F-Ch-PET/CT, which proved more sensitive than 18F-FDG PET/CT in our patient, in NETs. Further investigation is warranted.

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