Case Report

Paradoxal metabolic flare detected by 18F-fluorodeoxyglucose positron emission tomography in a patient with metastatic breast cancer treated with aromatase inhibitor and biphosphonate

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ABSTRACT

Patients with estrogen-receptor-positive advanced breast cancer are treated with endocrine therapy. The majority of breast cancer localizations show 18F-fluorodeoxyglucose (FDG) uptake at positron emission tomography (PET) examination. In these patients, the metabolic flare after therapy is common and was proposed as an index of therapy efficacy. Nevertheless, prolonged persistence of flare can lead to misinterpretation. We describe a case of a patient with invasive ductal breast cancer with bone metastases at bone scintigraphy and FDG PET scan and with expression of estrogen receptors. Initially, the patient underwent endocrine therapy in addition to a biphosfonate. Owing to progression observed in a bone scan, Tamoxifen was substituted with aromatase inhibitors. Successive bone scan examinations showed stabilization with a marked clinical improvement. A second FDG PET was performed 28 months after the first examination and showed a metabolic flare phenomenon with concomitant partial calcification of osteolitic lesions. This is an unusual case of prolonged metabolic flare.

Keywords: 18F-fluorodeoxyglucose, aromatase inhibitor, biphosfonate, breast cancer, response evaluation

INTRODUCTION

The management of patients with metastatic breast cancer is facilitated by the availability of the most effective systemic therapies.[1,2] In particular, the endocrine treatment allows to reduce estrogen production, block signaling through estrogen receptor (ER) or antagonize ER itself.

Positron emission tomography (PET) scan examination with 18F-fluorodeoxyglucose (FDG PET) can measure tumor glycolysis, which may be considered an indirect measure of cell proliferation.[3] Serial FDG PET can be used for the detection of response to chemotherapy in several tumors, including breast.[4-7]

A paradoxical increase at FDG PET examination of bone metastases metabolic activity, which is subsequent to endocrine treatment has been proposed as an index of therapy efficacy.[8] This occurrence in a bone scan is well-known as "flare phenomenon."

Although the early appearance of flare at PET is a positive prognostic marker, prolonged persistence of this phenomenon could eventually disturb the correct image interpretation.[9]

CASE REPORT

Here we report a case of a 53-year-old woman suffering from advanced breast cancer with bone pain, who came to our observation for the first time in July 2010 in Cracow branch of MSC Memorial Cancer Center. Routine radiological and scintigraphic bone examination confirmed multifocal bone spread with a mixed osteolytic-osteosclerotic pattern [Figure 1].

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Biphosphonate (Aredia 90 mg/4 weeks) and endocrine treatments were immediately started (Zoladex 3.6 mg/month and Tamoxifen 20 mg/day) together with palliative radiotherapy of left hemipelvis.

The first FDG PET scan was ruled out in Gliwice branch of our institution on October 1, 2010 in order to exclude metastatic spread to soft-tissues. It was performed with the use of a Philips Gemini GXL device, 60 min after an injection of 333 MBq of radiotracer. Numerous skeletal lesions were detected, with no metastases outside bones [Figure 2a].

A bone scan showed progression in April 2011. Due to clinical worsening of the patient's condition, with Zubrod score having increased from 2 to 3, Tamoxifen was substituted with an aromatase inhibitor (Femara 2.5 mg/day). The second palliative radiotherapy was performed on the thoracic spine from April to May 2011.

A clinical improvement was observed successively in September 2011, with Zubrod score having returned to 2 and a stable bone scan.

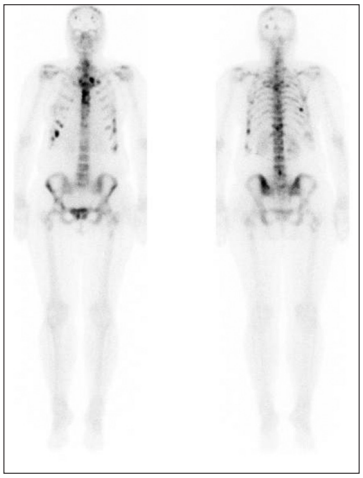

Figure 1: First bone scan performed on July 2010, showing bone metastases

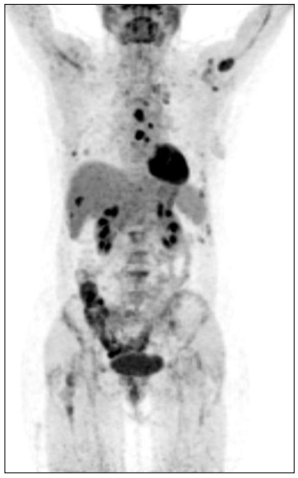

Figure 2: (b) Second fluorodeoxyglucose positron emission tomography from 8 February 2013: Maximum intensity projection projection showing a marked increase of metabolism in sternal, humeral and costal lesions

In March 2012, Zubrod score shifted down further to 1 and Zoladex were stopped. The patient got only bifosphonate and aromatase inhibitor treatment.

Another FDG PET examination was performed on February 8, 2013 for a complexive evaluation of the regression degree, 22 and 31 months after the beginning of therapies with the aromatase inhibitor and biphosphonate respectively. The scan was ruled out with the use of a Siemens mCT device, 1 h after an injection of 240 MBq of FDG. Evident recalcification of bone lesions was seen on computed tomography (CT), while an increase of FDG uptake was clearly observable for almost all the bone lesions [Figures 2b, 3 and 4]. A direct comparison between SUV scores was not possible, because of PET scans having been performed by different devices. However, tumor/background ratios between physiological liver uptake and pathologic FDG accumulation displayed on Figures 3b (V right rib) and 4b (sternum) confirmed the visual impression of increased radiofarmaceutical uptake [Table 1].

DISCUSSION

It has been demonstrated that the metabolic flare detected in the FDG PET scan after endocrine therapy was due to initial estrogen-like agonist effects, which were induced by increased

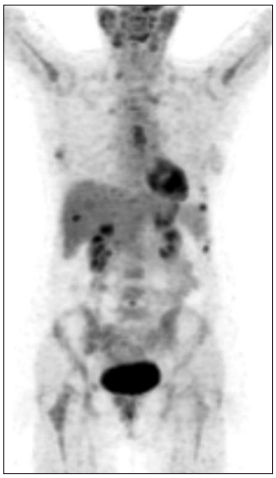

Figure 2: (a) First 18F-fluorodeoxyglucose positron emission tomography performed on 1st October 2010: Maximum intensity projection projection with some pathological uptakes in the sternum, ribs, both humeri and right femur

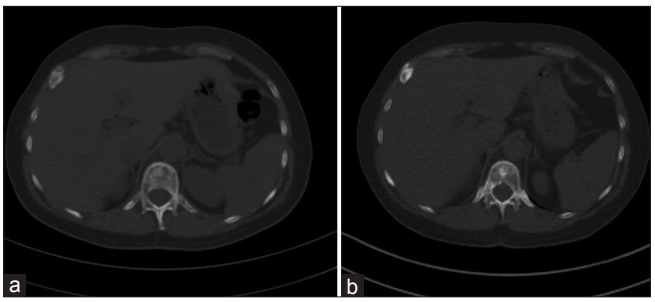

Figure 3: (a and b) Mixed osteolytic-osteosclerotyc lesion on VIII right rib at firs positron emission tomography-computed tomography examination (a) showing recalcification at second examination (b)

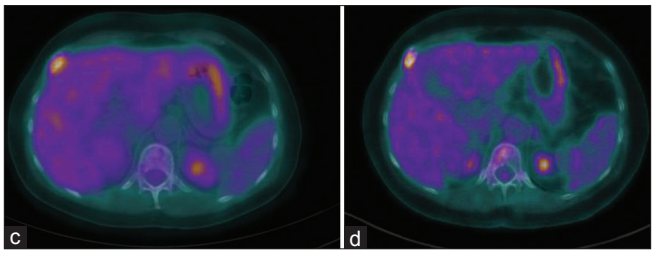

Figure 3: (c and d) Fused images of costal lesion at first (c) and second (d) positron emission tomography-computed tomography examination, showing 18F-fluorodeoxyglucose uptake increase concomitant to recalcification

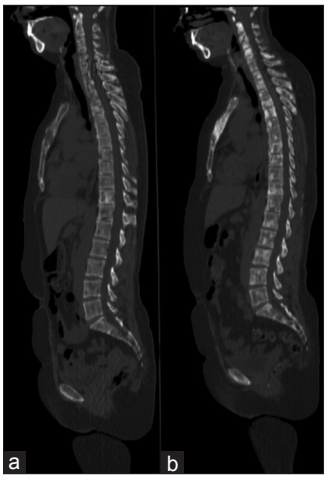

Figure 4: (a and b) Sagittal computed tomography (CT) projection with vertebral and sternal lesions at firs positron emission tomography-CT examination (a) showing recalcification at second examination (b)

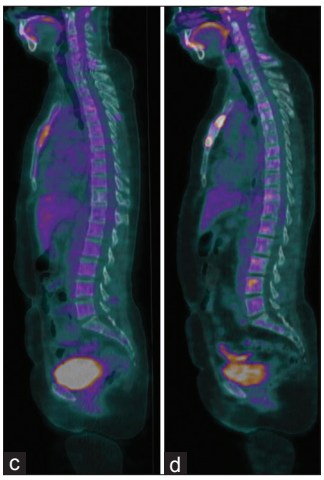

Figure 4: (c and d) Positron emission tomography-computed tomography (PET-CT) fused images of vertebral and sternal 18F-fluorodeoxyglucose (FDG) uptakes at first (c) and second (d) PET-CT examination, showing FDG uptake increase and recalcification

levels of the hormone. Based on this fact, some authors suggested clinical use of an increase of FDG uptake as an early biomarker of endocrine therapy efficacy.[8]

The metabolic flare was also reported to possibly be a result of biphosphonate treatment of metastatic breast cancer.[10]

Table 1: SUVs of the bone lesion at baseline PET examination (t0), at second PET scan (t1) and its ratios with physiological liver uptake

Organ	SUV_{max} t_0	SUV_{max} t_1	Lesion/ liver ratio t_0	Lesion/ liver ratio t_1	Ratio increase %
Healthy liver	2.63	3.3			
V right rib	3.47	5.05	1.31	1.66	+21
Sternum	3.8	10.22	1.44	3.09	+114

SUV: Standard uptake value, PET: Positron emission tomography

On the other hand, other authors proposed a different approach taking into account the fact that the level of glucose metabolism in malignancies is strongly related to the expression of antigen Ki-67. Since an early decrease of Ki-67 expression after aromatase inhibitor therapy is a correlate with a better prognosis,[9] it was suggested that a decrease of FDG uptake could be adopted as a non-invasive biomarker of aromatase inhibitors efficacy.[7]

Patient we described had breast cancer metastatic to bones and was treated with a biphosphonate and an aromatase inhibitor, which is a standard therapeutic procedure in such cases. It was a completely unexpected finding to observe the presence of the metabolic flare about 2 and 2.5 years after starting therapies with aromatase inhibitor and bisphosphonate respectively. After having been diagnosed, the patient was initially treated also with Tamoxifene and Zoladex. It is important to underline that the treatment was changed between the initial and the second PET studies and one can eventually speculate that the metabolic progression at second PET is due to the discontinuation of the first-line therapy. Nonetheless, if the minor degree of FDG uptake at first examination was due to major efficacy of initial treatment, we should expect worsening of patient's condition parallel to metabolic progression of the disease. The clinical improvement with evidence of bone healing in this timeframe makes this theory less likely: The unexpected increase in FDG uptake discordant with all other clinical and radiological data should be explained mainly by metabolic flare. In our case the drugs responsible for this phenomenon are the aromatase inhibitor and/or the biphosphonate, despite the long time elapsed from their initiation. Unfortunately, the patient had no further PET scan in the follow-up; therefore, the presence of metabolic flair should be regarded as a hypothesis, since one cannot exclude in advance a disease progression as underlying cause of increased FDG uptake.

We did not find literature data about persistent or tardive metabolic flare, thus our case should be considered when evaluating the role of PET-FDG as a biomarker of therapy efficacy.

Finally, our case underlines the pivotal role of an accurate evaluation of the CT scan when PET is performed by a hybrid PET-CT device. The detection of recalcification, together with clinical improvement is the most important elements indicating the reparative character of the increase of FDG uptake in bone lesions. Failing to interpret this radiological feature correctly by a reporting doctor can lead to an erroneous description of increased FDG uptake as indicative of progressive disease.

REFERENCES

1. Chia SK, Speers CH, D'yachkova Y, Kang A, Malfair-Taylor S, Barnett J, *et al.* The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. Cancer 2007;110:973-9.
2. Barrios C, Forbes JF, Jonat W, Conte P, Gradishar W, Buzdar A, *et al.* The sequential use of endocrine treatment for advanced breast cancer: Where are we? Ann Oncol 2012;23:1378-86.
3. Nguyen QD, Aboagye EO. Imaging the life and death of tumors in living subjects: Preclinical PET imaging of proliferation and apoptosis. Integr Biol (Camb) 2010;2:483-95.
4. Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: Initial evaluation. J Clin Oncol 1993;11:2101-11.
5. Kawada K, Murakami K, Sato T, Kojima Y, Ebi H, Mukai H, *et al.* Prospective study of positron emission tomography for evaluation of the activity of lapatinib, a dual inhibitor of the ErbB1 and ErbB2 tyrosine kinases, in patients with advanced tumors. Jpn J Clin Oncol 2007;37:44-8.
6. Dunnwald LK, Gralow JR, Ellis GK, Livingston RB, Linden HM, Specht JM, *et al.* Tumor metabolism and blood flow changes by positron emission tomography: Relation to survival in patients treated with neoadjuvant chemotherapy for locally advanced breast cancer. J Clin Oncol 2008;26:4449-57.
7. Kurland BF, Gadi VK, Specht JM, Allison KH, Livingston RB, Rodler ET, *et al.* Feasibility study of FDG PET as an indicator of early response to aromatase inhibitors and trastuzumab in a heterogeneous group of breast cancer patients. EJNMMI Res 2012;2:34.
8. Mortimer JE, Dehdashti F, Siegel BA, Trinkaus K, Katzenellenbogen JA, Welch MJ. Metabolic flare: Indicator of hormone responsiveness in advanced breast cancer. J Clin Oncol 2001;19:2797-803.
9. Tu DG, Yao WJ, Chang TW, Chiu NT, Chen YH. Flare phenomenon in positron emission tomography in a case of breast cancer – A pitfall of positron emission tomography imaging interpretation. Clin Imaging 2009;33:468-70.
10. Chavdarova L, Piperkova E, Tsonevska A, Timcheva K, Dimitrova M. Bone scintigraphy in the monitoring of treatment effect of bisphosphonates in bone metastatic breast cancer. J BUON 2006;11:499-504.

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