Unexpected Second Primary Malignancies Detected by F-18 FDG PET/CT During Follow-up for Primary Malignancy: Two Case Reports

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Abstract As the survival rate of cancer patients has increased over the last few decades, the risk of cancer survivors developing second primary malignancies has gained attention. We report two rare cases of second primary hematologic malignancy detected by ^{18}F -fluorodeoxyglucose (F-18 FDG) positron emission tomography/computed tomography (PET/CT) during follow-up for primary solid malignancies. Acute lymphoblastic leukemia developed in a breast cancer patient and non-Hodgkin lymphoma in an anal cancer patient. F-18 FDG PET/CT findings led to the diagnosis of unexpected second primary hematologic malignancy in cancer survivors in these two cases.

Keywords F-18 fluorodeoxyglucose · Positron emission tomography · Second primary malignancy · Hematologic malignancy

Introduction

The role of ^{18}F -fluorodeoxyglucose positron (F-18 FDG) emission tomography/computed tomography (PET/CT) has expanded extensively in oncology because of excellent sensitivity and specificity [1–3]. As a result, incidental detection of unexpected second primary malignancies not found by conventional imaging modalities has also increased. In one study, F-18 FDG PET/CT detected unexpected second F-18 FDG-avid malignancies in at least 1.2 % of patients [4].

Here, we report the cases of two cancer survivors with rare second primary hematologic malignancies detected by F-18

FDG PET/CT scans. Case 1 is a woman with underlying breast cancer who developed acute lymphoblastic leukemia and case 2 is a man with underlying anal cancer who developed B-cell lymphoma.

Case Reports

Case 1

A female patient was diagnosed with invasive ductal carcinoma of the right breast at the age of 46 years in August 2007. She received neoadjuvant chemotherapy with six cycles of PGH (paclitaxel, gemcitabine, and trastuzumab) and was treated with partial mastectomy and axillary lymph node dissection. She received adjuvant radiation therapy and tamoxifen for 1 year. Two years after the surgery, ductal carcinoma in situ was found in the same breast, and she received simple mastectomy and letrozole for 27 months. There had been no evidence of recurrence or other malignancy on annual routine follow-up with F-18 FDG PET/CT scan, enhanced chest CT, and Tc-99 m methylene diphosphonate bone scan until September 2013 and. In March 2014, routine F-18 FDG PET/CT scan incidentally detected intense hypermetabolism along the bone marrow (BM) of the whole axial and proximal appendicular skeleton and multiple hypermetabolic lymph nodes in the left neck, axilla, mediastinum, retroperitoneum, and both common iliac areas (Fig. 1). Peripheral blood analysis revealed a white blood cell count of $36,620/\mu\text{L}$ with 77 % blasts, a hematocrit of 31.4 %, hemoglobin level of 10.4 g/dL, and $21,000$ platelets/ μL . A BM study revealed an infiltrate composed of approximately 97 % leukemic blasts with suppressed trilineage hematopoiesis, which indicated acute lymphoblastic leukemia (ALL). BM immunophenotyping revealed blasts expressing B-cell markers including CD10,

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Fig. 1 Serial images of F-18 FDG PET/CT scan of the patient in case 1. **a** On initial F-18 FDG PET/CT scan for diagnosis of breast cancer, a hypermetabolic mass in the right breast and hypermetabolic lymph nodes in the right axilla were observed (*solid arrows*). **b** No abnormal hypermetabolic lesion was found to suggest recurrence or other malignant process on follow-up F-18 FDG PET/CT scans for 6 years after diagnosis

of the primary breast cancer. **c** Seven years after diagnosis of the primary breast cancer, intense hypermetabolism was incidentally noted along the bone marrow of the whole axial and proximal appendicular skeleton, with several hypermetabolic lymph nodes, on routine F-18 FDG PET/CT follow-up scan. The patient was finally diagnosed with leukemia

CD19, CD20, CD34, and terminal deoxynucleotidyl transferase. The karyotype was 46, XX, t(9;22)(q34;q11.2) [14]/46,XX [6]. Chromosome analysis by fluorescence in situ hybridization (FISH) showed BCR/ABL1 rearrangement and reverse-transcriptase nested polymerase chain reaction (RT-nested PCR) showed a positive result of minor BCL/ABL rearrangement (e1a2 type). Based on the BM study, the patient was diagnosed with Philadelphia chromosome-positive B-lymphoblastic leukemia. She received chemotherapy consisting of VPDL (vincristine, prednisolone, daunorubicin, and L-asparaginase) and intrathecal methotrexate due to central nervous system involvement.

Case 2

A male patient was diagnosed with anal cancer in May 2009 at the age of 70 years. He was treated with concurrent chemoradiotherapy with two cycles of FM (5-fluorouracil [5-FU], mitomycin-C) and radiation to the anus (totaling 5,580 cGy) and both inguinal areas (totaling 2,860 cGy each). He had been in continuous complete remission since 2009. In March 2013, enhanced chest CT scan for regular follow-up showed a nodule in the right lower lung. With the suspicion of a primary lung cancer, the patient underwent F-18 FDG PET/CT scan for further evaluation. The F-18 FDG PET/CT scan revealed hypermetabolism in the lower right lung nodule; multiple lymphadenopathies with hypermetabolism in both neck chains, the mediastinum, the retroperitoneum, the mesentery, and both iliac chains; splenomegaly with hypermetabolism;

and inhomogeneous hypermetabolism along the BM in the whole axial and proximal appendicular skeleton (Fig. 2). These findings suggested hematologic malignancy such as lymphoma rather than primary lung malignancy. Results from neck lymph node biopsy led to a final diagnosis of malignant lymphoma of B-cell lineage. A BM study indicated BM involvement by lymphoma. He was treated with steroids, but refused further treatment because of his poor general condition and died of tumor lysis syndrome.

Discussion

A second primary malignancy is defined as a malignancy developing subsequent to the primary malignancy; it could be related to the pre-existing malignancy but is not a recurrence or metastasis of the primary malignancy [5]. Because of the increased survival rate of cancer patients over the last few decades [6], second primary malignancies in cancer survivors have gained attention as another disease burden in current medicine [7]. According to the NCI's Surveillance, Epidemiology and End Results (SEER) Program, there is a 14 % higher risk of a second primary malignancy in cancer survivors than in the general SEER population [8].

There are several hypotheses regarding the increased prevalence of second primary malignancy in cancer survivors based on shared risk factors such as environment carcinogens, genetic susceptibility, infection, immunosuppression, and previous cancer therapy effect [8]. Although establishing the exact

Fig. 2 Serial images of F-18 FDG PET/CT scan of the patient in case 2. **a, b** On initial F-18 FDG PET/CT scan for diagnosis of primary anal cancer, a hypermetabolic lesion was noted at the anus (*solid arrow*). **c** Four years after diagnosis of the primary anal cancer, a nodule in the lower lobe of the right lung was observed and this nodule showed hypermetabolism on F-18 FDG PET/CT scan. In addition to this, he

developed multiple lymphadenopathies with hypermetabolism both above and below the diaphragm, splenomegaly with hypermetabolism, and inhomogeneous hypermetabolism along the whole axial and appendicular skeleton. The patient was finally diagnosed with malignant lymphoma

etiology of second primary malignancies is difficult, it is well accepted that several types of chemotherapeutic drugs—such as alkylating agents, DNA topoisomerase, and, less frequently, antimetabolites—and radiotherapy increase risks for development of a second primary malignancy [9–13]. Acute myeloid leukemia (AML) is the most common form of therapy-related hematologic malignancy [9]. Second primary ALL is much rarer than AML, with about ten cases having been reported. Two of these case reports were ALL with t(9:22)(q34;q11.2) in prior breast cancer patients similar to our first case [14, 15]. In the SEER cancer registries, a fivefold increase of secondary non-Hodgkin lymphoma (NHL) was reported in anal cancer patients less than 50 years of age in association with HIV infection [3]. In contrast, the patient in our second case was over 50 years old and without HIV infection.

The patients in our cases were treated with both chemotherapy and radiotherapy. The patient in the first case received six cycles of neoadjuvant chemotherapy for breast cancer, including the antimetabolite gemcitabine and the mitotic inhibitor paclitaxel, as well as postoperative radiotherapy. The patient in the second case received concurrent chemoradiotherapy using the antimetabolite 5-FU and the anthracycline mitomycin-C for anal cancer. However, because many factors contribute to the development of hematologic malignancy as described above, it cannot be determined whether the secondary malignancies in our cases are related to prior chemotherapy or radiotherapy or arose *de novo*.

To the best of our knowledge, this is the first case report describing the use of F-18 FDG PET/CT for diagnosing a

second primary hematologic malignancy in cancer survivors. There have been some reports of second primary malignancies detected on the F-18 FDG PET/CT scans. However, those were limited to solid tumors [16–19]. Hematologic malignancy is difficult to detect with conventional CT images because it is a systemic disease that can present without definite anatomical change. In the first case, there were no definite anatomical abnormalities, with some indeterminate sized lymph nodes and no symptoms reported by the patient. However, F-18 FDG PET/CT showed hypermetabolism in the bone marrow and lymph nodes, leading to early diagnosis and early treatment. In the second case, a lung mass was detected with conventional CT imaging, mimicking metastasis from anal cancer or primary lung cancer. However, F-18 FDG PET/CT showed additional abnormalities outside the chest, suggesting systemic malignant involvement rather than a solid tumor.

In summary, we report two rare cases in which second primary hematologic malignancies were diagnosed, ALL in a breast cancer patient and NHL in an anal cancer patient, using F-18 FDG PET/CT. F-18 FDG PET/CT could be helpful not only in detecting recurrence but also in identifying second primary malignancies, including hematologic malignancies. Considering the conventional imaging for cancer surveillance generally focuses on the restricted anatomical area, whole body F-18 FDG PET/CT scan would be a useful surveillance tool for young cancer survivors, who have higher risk of malignancy than the general population [8]. Future studies for efficacy and cost-effectiveness of surveillance by F-18 FDG PET/CT scan on cancer survivor are warranted.

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Informed Consent All procedures followed were performed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000. The study design and exemption of informed consent were approved by the Institutional Review Board of the National Cancer Center.

Conflict of Interest Ji-In Bang, Eun Seong Lee, Tae-Sung Kim, and Seok-Ki Kim declare that they have no conflicts of interest.

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