**Diffuse bone marrow uptake related to granulocyte colony-stimulating factor-producing maxillary sinus carcinoma on 4-borono-2-\(^{18}\)F-fluoro-L-phenylalanine positron emission tomography/computed tomography**

**ABSTRACT**
Granulocyte colony-stimulating factor (G-CSF) can be produced by tumor cells and is known to promote tumor growth, thereby potentially accelerating disease progression. Squamous cell carcinoma (SCC) at maxillary sinus is aggressive growth with poor prognosis. Maxillary sinus carcinomas are rare and can be clinically silent in the early stages or manifest with the same signs and symptoms of more common illnesses, leading to their delayed diagnosis of disease. Hypermetabolic uptake of \(^{18}\)F-fluorodeoxyglucose (\(^{18}\)F-FDG) but not of 4-borono-2-\(^{18}\)F-fluoro-L-phenylalanine (\(^{18}\)F-FBPA), in the bone marrow of patients with G-CSF-producing tumors without bone marrow involvement during positron emission tomography (PET), has been reported. The present case report describes our first experience of bone marrow uptake in PET/computed tomography examination using \(^{18}\)F-FBPA, high uptake seen in the bone marrow of a patient with a G-CSF-secreting SCC of the maxillary sinus that it relapsed following chemoradiation therapy and surgical resection of the tumor.

**Keywords:** \(^{18}\)F-4-borono-2-\(^{18}\)F-fluoro-L-phenylalanine, bone marrow uptake, GSF, maxillary squamous carcinoma

**INTRODUCTION**
Granulocyte colony-stimulating factor (G-CSF) is a growth factor and causes tumor cells to proliferate.\(^{[1-4]}\) In the squamous cell carcinoma (SCC) of the maxillary sinus, G-CSF secretion by tumor cells can thus worsen the prognosis of an aggressive tumor.\(^{[3,4]}\) Here, we report a case of a 70-year-old female with relapsed G-CSF-secreting SCC of the maxillary sinus after chemoradiation therapy (CRT). The increase in blood G-CSF levels in this patient reflected the degree of disease progression. It also corresponded to the degree of diffuse bone marrow uptake of 4-borono-2-\(^{18}\)F-fluoro-L-phenylalanine (\(^{18}\)F-FBPA) as well as of\(^{18}\)F-fluorodeoxyglucose (\(^{18}\)F-FDG) in the positron emission tomography/computed tomography (PET/CT) scans. The degree of uptake of\(^{18}\)F-FBPA in the bone marrow is usually minimal in patients with non-G-CSF-secreting tumors that have not metastasized to the bone; hence, this occurrence is rare.

**Kharisma Perdani Kusumahstuti\(^{1,2}\), Tadashi Watabe\(^{1,3}\), Naoya Kitamura\(^{4}\), Tetsuya Yamamoto\(^{4}\)**

\(^{1}\)Department of Nuclear Medicine and Tracer Kinetics, Graduate School of Medicine, Osaka University, Osaka, Japan; \(^{2}\)Department of Nuclear Medicine and Molecular Imaging, Universitas Padjadjaran, General Hasan Sadikin Hospital, Bandung, Indonesia; \(^{3}\)Institute for Radiation Sciences, Osaka University, Suita, Osaka, \(^{4}\)Department of Oral and Maxillofacial Surgery, Kochi Medical School, Kochi University, Nangoku, Kochi, Japan

**Address for correspondence:** Dr. Tadashi Watabe, Department of Nuclear Medicine and Tracer Kinetics, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan. E-mail: watabe@tracer.med.osaka-u.ac.jp

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CASE REPORT

A 70-year-old female, spuriously diagnosed with maxillary sinusitis, underwent CT, which showed maxillary osteomyelitis and a mass projecting into her right maxillary sinus and right nasal cavity. Two months later, she underwent surgery with resection of a solid tumor at the maxillary antrum, later revealed to be a G-CSF-producing SCC (Stage IVA, T4N0M0). Two weeks after surgery, there was a considerable increase in diffuse bone marrow uptake of $^{18}$F-FDG in the $^{18}$F-FDG PET-CT scan despite lack of bone marrow involvement as evidenced by the bone marrow biopsy [Figure 1a and b]. In addition, there was a marked increase in the white blood cell count (WBC) from $50.1 \times 10^3$ cells/$\mu$L to $106.3 \times 10^3$ cells/$\mu$L; blood G-CSF from 757 pg/mL to 2290 pg/mL; and alkaline phosphatase (ALP) from 655 pg/mL to 2339 pg/mL, 1 month following the surgery. Subsequently, the patient was given postoperative CRT, which consisted of superselective intra-arterial chemotherapy (cisplatin [CDDP] 130 mg, 5 times) and radiation therapy (total 60 Gy). During CRT, the WBC, G-CSF, and ALP levels gradually decreased to $64.1 \times 10^3$ cells/$\mu$L, 1330 pg/mL, and 1571 U/L, respectively.

Six months after CRT, the patient’s G-CSF levels, ALP levels, and WBC count increased to 875 pg/mL, 673 U/L, and $45.5 \times 10^3$ cells/$\mu$L, respectively, suggesting recurrence. This was confirmed with an $^{18}$F-FDG PET scan, which showed a hypermetabolic area at the former operation site. In addition, the $^{18}$F-FDG PET scan showed a mild diffuse bone marrow uptake of $^{18}$F-FDG [Figure 1c and d]. $^{18}$FBPA PET/CT taken 8 months after CRT for pretreatment evaluation for boron neutron capture therapy (BNCT) showed a similar uptake pattern of $^{18}$F-FBPA in the former operation site but a diffuse intense uptake of $^{18}$F-FBPA in the bone marrow. This increased bone marrow uptake of $^{18}$F-FBPA occurred in the absence of bone marrow metastases. The uptake of $^{18}$F-FBPA seen in the bone marrow could be attributed to the increased levels of G-CSF, which also caused an increase in WBCs [Figure 2].

$^{18}$F-FBPA-PET study was performed with the approval of the Ethics Committee of Osaka University Hospital. Written informed consent was obtained from the patient.

DISCUSSION

This report presents a patient with a G-CSF-producing squamous carcinoma in the maxillary sinus showing diffuse bone marrow uptake of $^{18}$F-FBPA on the $^{18}$F-FBPA PET scan. This uptake of $^{18}$F-FBPA in the bone marrow in the absence of bone marrow metastases is rare because $^{18}$F-FBPA is highly suited for targeting G-CSF producing tumors.
specific to metastatic cancer cells since it is a substrate of L-type amino acid transporter 1 (LAT1). Since the uptake of $\text{^{18}F}$-FBPA in inflamed and reactive tissue is minimal, we usually do not see false-positive uptakes in the bone marrow. It is not necessary to perform bone marrow biopsy in a case with diffuse bone marrow uptakes with increased G-CSF level. We can differentiate it from metastasis, which usually showed focal or heterogeneous uptakes.

Maxillary sinus carcinomas are rare and can be clinically silent in the early stages. At the time of diagnosis, 70%–80% of maxillary sinus carcinomas are already at the T3 or T4 stages with local tumor extension. The overall mortality rate of these tumors is 65.5%, and the overall 1-, 2-, and 5-year survival rate is 57.9%, 44.8%, and 17.7%, respectively. This patient was initially diagnosed with maxillary sinusitis.

G-CSF-producing cells are rarely associated with head-and-neck carcinomas. Asano et al. reported the first case of a G-CSF-producing tumor and proposed the following criteria for diagnosing G-CSF-producing tumors: (1) leukocytosis with neutrophil predominance; (2) elevated serum and urine G-CSF levels; (3) normalization of WBC count and serum G-CSF level after removal of the tumor; and (4) increased G-CSF in tumor tissues. The gold standard to diagnose of G-CSF-producing tumor in this case was the laboratory finding. It showed elevated WBC and G-CSF levels, which were accompanied by normalization after the CRT and increase at the recurrence.

Glioblastoma, melanoma, and head-and-neck tumors can be treated successfully with BNCT. Here, a $\text{^{10}B}$-tagged tumor-seeking compound administered to patients accumulates in the tumors. A beam of thermal neutrons directed at the tumor causes nuclear capture of neutrons by boron, leading to nuclear fission. The tumors get irradiated by the reaction of $\text{^{10}B}$ (n,α) $\text{^7Li}$. Therapeutic efficacy to BNCT can be predicted by $\text{^{18}F}$-FBPA PET since the uptake pattern is similar to the $\text{^{10}B}$-tagged compounds administered during BNCT. This patient had thus undergone $\text{^{18}F}$-FBPA PET for pretreatment evaluation of BNCT, enabling us to make these observations.

Hypermetabolic bone marrow uptake of $\text{^{18}F}$-FDG can be caused by increased metabolic activity in bone marrow, which is evidenced by increased G-CSF and WBC levels. Depending on the red marrow activity, the uptake can vary from moderate to intense. In the present study, increased bone marrow uptake of $\text{^{18}F}$-FBPA was seen as well. G-CSF tumors can sometimes cause this to occur possibly through an amino acid transporter.

We performed FDG PET/CT before 1st CRT and 6 months after CRT. FBPA PET/CT was performed 2 months after the 2nd FDG PET/CT. Both FDG and FBPA showed diffuse bone marrow uptake and high uptake in the recurrent tumor. However, FBPA-PET showed increased uptakes in the bilateral humerus and femur compared to FDG-PET, suggesting progression during the interval between the two scans.

Tani et al. showed a significant correlation between $\text{^{18}F}$-BPA and $\text{^{18}F}$-FDG uptake in head-and-neck cancers. This was seen in our patient as well. Uptake of $\text{^{18}F}$-FBPA occurs through LAT1, which is present predominantly in malignant cells and is highly selective. $\text{^{18}F}$-FBPA usually shows minimal uptake in normal bone marrow [Figure 3]. However, in this patient, the $\text{^{18}F}$-FBPA PET scan showed homogeneous uptake of $\text{^{18}F}$-FBPA despite bone marrow biopsy ruling out bone marrow metastases. Thus, this case illustrates that a G-CSF-producing tumor should be considered if increased uptake of $\text{^{18}F}$-FBPA in the bone marrow is seen on the $\text{^{18}F}$-FBPA PET scan in the absence of bone marrow metastases.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.
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Conflicts of interest
There are no conflicts of interest.

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