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Case Report

Usefulness of ^{11}C-Methionine Positron Emission Tomography for Monitoring of Treatment Response and Recurrence in a Glioblastoma Patient on Bevacizumab Therapy: A Case Report

Tomoyuki Nakano[a] Kaoru Tamura[a] Yoji Tanaka[a] Motoki Inaji[a, b] Shihori Hayashi[a, b] Daisuke Kobayashi[c] Tadashi Nariai[a, b] Jun Toyohara[b] Kenji Ishii[b] Taketoshi Maehara[a]

[a]Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo, Japan; [b]Research Team for Neuroimaging, Tokyo Metropolitan Institute of Gerontology, Tokyo, Japan; [c]Department of Human Pathology, Tokyo Medical and Dental University, Tokyo, Japan

Keywords

^{11}C-methionine positron emission tomography · Bevacizumab · Glioblastoma · Recurrence · Vascular endothelial growth factor

Abstract

Recently developed molecular targeted therapies such as bevacizumab (BEV; Avastin) therapy have therapeutic efficacy for glioblastoma. However, it is difficult to distinguish between a tumor response and nonenhancing tumor progression with conventional magnetic resonance imaging (MRI) after BEV administration. Here we present a recurrent glioblastoma case in which ^{11}C-methionine positron emission tomography (MET-PET) provided useful information for detecting tumor recurrence after complete remission, as assessed by the Response Assessment in Neuro-Oncology criteria. A 47-year-old male with a left frontal lobe glioblastoma ex-

Kaoru Tamura, MD, PhD
Department of Neurosurgery
Tokyo Medical and Dental University
1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519 (Japan)
E-Mail tamura.nsrg@tmd.ac.jp

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perienced recurrence 6 months postoperatively. We administered BEV concomitantly with temozolomide, subsequent to gamma knife surgery. Two months after starting BEV, complete remission was obtained. MET uptake on PET gradually decreased and had nearly disappeared 4 months after initiating BEV. No enhanced area was seen on MRI for 17 months after BEV initiation. Nevertheless, MET-PET revealed recurrence, visualized as nonenhancing tumor progression. MET-PET provides useful information for detecting glioblastoma recurrence, which lacks contrast enhancement on MRI after BEV therapy.

Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults. Current treatment regimens that include daily temozolomide (TMZ) and radiotherapy followed by maintenance TMZ have significantly improved survival of patients with newly diagnosed GBM as compared to radiotherapy alone [1]. Nevertheless, GBM patients have a poor prognosis, with a median survival of only 14.6 months.

As GBM proliferates rapidly by collecting a rich blood supply due to tumor angiogenesis, antiangiogenic approaches offer an attractive treatment strategy. Recent developments in molecular targeted therapy have produced effective drugs such as bevacizumab (BEV; Avastin) [2]. Focusing on the intense angiogenesis and high expression level of vascular endothelial growth factor (VEGF) in GBM, BEV is a monoclonal antibody against VEGF that blocks neoangiogenesis within the tumor [2]. BEV dramatically reduces gadolinium-enhanced lesions on magnetic resonance imaging (MRI) and prolongs progression-free survival [3, 4]. However, despite the recent progress in chemotherapeutic regimens, GBM still has a high recurrence rate and the prognosis remains poor; overall survival has not been changed by BEV [3, 4].

Currently, MRI, including contrast-enhanced T1-weighted and T2/FLAIR (fluid-attenuated inversion recovery) imaging, is used to evaluate antiangiogenic treatment responses [5]. However, by restoring the blood-brain barrier (BBB), BEV may reduce T1 contrast enhancement and T2/FLAIR hyperintensity, thereby obscuring the imaging-based detection of progression [5]. Therefore, innovative imaging strategies are needed.

^{11}C-methionine (MET) is an amino acid tracer used to evaluate the tumor distribution on positron emission tomography (PET) [6]. Gadolinium-enhanced lesions represent the tumor area in which the BBB has collapsed, whereas MET passes through the normally functioning BBB via the neutral amino acid transporter, allowing the tumor tissue beyond the enhanced portion of the tumor to be detected [7]. Much higher MET accumulation is seen in tumors than in normal brain tissue [6]. Hence, MET-PET is a useful neuroimaging technique for defining the boundaries of high-grade gliomas without obstruction of the BBB, and allows earlier and more accurate delineation of tumor extension than computed tomography or conventional MRI [6, 7].

Herein, we report a recurrent GBM case in which MET-PET provided useful information by delineating nonenhanced tumor recurrence after BEV administration.

Case Presentation

A 47-year-old male patient presented to our hospital with Broca's aphasia and memory disturbance. MRI revealed a 4-cm-diameter ring-enhanced cystic mass lesion with perifocal

edema in the left frontal lobe (Fig. 1a). MET-PET showed high methionine uptake in the gadolinium-enhanced lesion (Fig. 1a). Since the tumor was located adjacent to the arcuate fasciculus and pyramidal tract, the patient underwent partial resection, and a diagnosis of GBM was confirmed histopathologically (Fig. 2a–c). Immunohistochemical staining demonstrated absence of mutant IDH-1 (R132H) and a high MIB-1 index (38.6%; Fig. 2d). Methylation of the O^6-methylguanine-DNA methyltransferase (MGMT) was identified by pyrosequencing.

Postoperatively, the patient underwent radiotherapy (fractionated extended focal irradiation in daily fractions of 2 Gy for a total of 54 Gy) and concomitant TMZ therapy (75 mg/m^2 daily for 42 days), followed by adjuvant TMZ treatment (150–200 mg/m^2 for 5 days every 28 days). Six months after the initial operation, his dysphasia had worsened, and right hemiparesis and simple partial seizures appeared. The follow-up MRI revealed tumor recurrence (Fig. 1b). Gamma knife stereotactic radiosurgery was performed for the recurrent lesion. BEV was then intravenously administered on an every-2-week schedule at a dose of 10 mg/kg, while the adjuvant TMZ was continued at a dose of 200 mg/m^2 for 5 days every 28 days.

After BEV administration, MRI showed dramatic weakening of the signal of the gadolinium-enhanced lesion. Two months of chemotherapy with BEV plus TMZ led to complete remission, as assessed by the Response Assessment in Neuro-Oncology (RANO) criteria (Fig. 1c) [5]. MET uptake on PET gradually decreased and had nearly disappeared after BEV initiation (Fig. 1c). The patient remained in a medically stable state, with no evidence of progression on MRI. Nevertheless, MET-PET revealed recurrence 17 months after the initiation of BEV, appearing as nonenhancing tumor progression (Fig. 1d). As MET accumulated in the primary motor cortex on the vertical side of the postoperative resection cavity, we decided not to remove the lesion. The patient was still followed up at our outpatient clinic, however, and gadolinium-enhanced T1-weighted imaging revealed rapid progression 22 months after completing administration of BEV (Fig. 3). The tumor crossed the midline via the corpus callosum, and multiple enhanced lesions were detected in the ipsilateral and contralateral hemispheres.

Discussion

To our knowledge, this is the first report of MET-PET detecting nonenhancing tumor recurrence after complete remission in a GBM patient receiving BEV treatment. When employing MRI after BEV treatment, it is difficult to distinguish between tumor response and nonenhancing tumor progression [5].

One of the factors accounting for the difficulty in assessing recurrence is the tumor's pathogenesis. Abundant angiogenesis around the tumor causes it to grow, and the tumor vessels mostly lack a functional BBB [7]. In addition, GBM is an aggressive malignancy that usually invades normal brain tissue, which makes the tumor boundary unclear [7]. The tumor cells spread around central nervous system tissues that contain a functional BBB. Intravenously administrated gadolinium leaks out from the collapsed BBB, so that MRI shows tumor enhancement [5]. Therefore, MRI with enhancement cannot detect tumor infiltration specifically, and this is a limitation to its use for evaluating tumors such as GBM.

Administration of an antiangiogenic agent such as BEV also results in an indistinct tumor distribution. Dramatic effects on vascular permeability cause limitations to the evaluation of recurrence in malignant glioma patients treated with BEV, because of the reduction of contrast enhancement. Moreover, de Groot et al. [8] described patients with non-contrast-enhancing progression who were receiving continuous treatment with an anti-VEGF agent, and they at-

tributed this to antiangiogenic therapy promoting the infiltration of tumor cells, based on histologic evidence obtained from recurrent high-grade glioma patients. Thus, BEV may change the permeability of vessels and precipitate GBM cell invasion.

A number of studies have examined neuroimaging techniques other than conventional MRI with the aim of identifying suspected glioma recurrences. Functional diffusion mapping MRI, dynamic susceptibility-weighted contrast-enhanced perfusion MRI, and dynamic contrast-enhanced MRI are alternative sequences for evaluating lesions [9]. Fluorodeoxyglucose, MET, FET (^{18}F-fluoroethyltyrosine), FLT (^{18}F-fluorothymidine), FDOPA (^{18}F-dihydroxyphenylalanine), and FMISO (^{18}F-fluoromisonidazole) are tracers used to perform PET for assessing malignant gliomas [10, 11]. Single-photon emission computed tomography is also performed to examine tumor distribution using thallium 201 (^{201}Tl) and iodine-123-methyltyrosine (^{123}I-IMT) [10]. Among these modalities, MET is the most clinically useful amino acid tracer, and a large body of evidence has been collected for central nervous system tumors [6]. A recent study has demonstrated MET-PET to be effective in differentiating brain radiation necrosis from tumor recurrence with high sensitivity and high specificity [12]. While the use of contrast agents is limited due to the aforementioned disruption of the BBB, MET can accumulate in tumor cells beyond the BBB via the neutral amino acid transporter [6]. Thereby, MET allows more accurate visualization of the distribution of tumor cells than does conventional MRI [7, 13]. This is why, in our present case, applying MET allowed us to detect nonenhanced recurrence of GBM much earlier than if we had used MRI alone.

On the other hand, since BEV is expected to be antiangiogenic rather than cytotoxic, the reason for the MET signal reduction on PET after BEV administration still remains uncertain. There are several reports that may explain this phenomenon. MET uptake correlated with microvessel density and the proliferative cell nuclear antigen index [14]. Furthermore, there is a reported correlation between MET accumulation and VEGF expression in patients with glioma [15]. Since molecular targeted anti-VEGF agents reduce VEGF expression and decrease the quantity of microvessels, BEV may reduce MET uptake on PET.

Conclusion

This report suggests that MET-PET is an effective neuroimaging technique for detecting nonenhanced recurrence of GBM after BEV therapy. Further study is needed to confirm our observations in this case.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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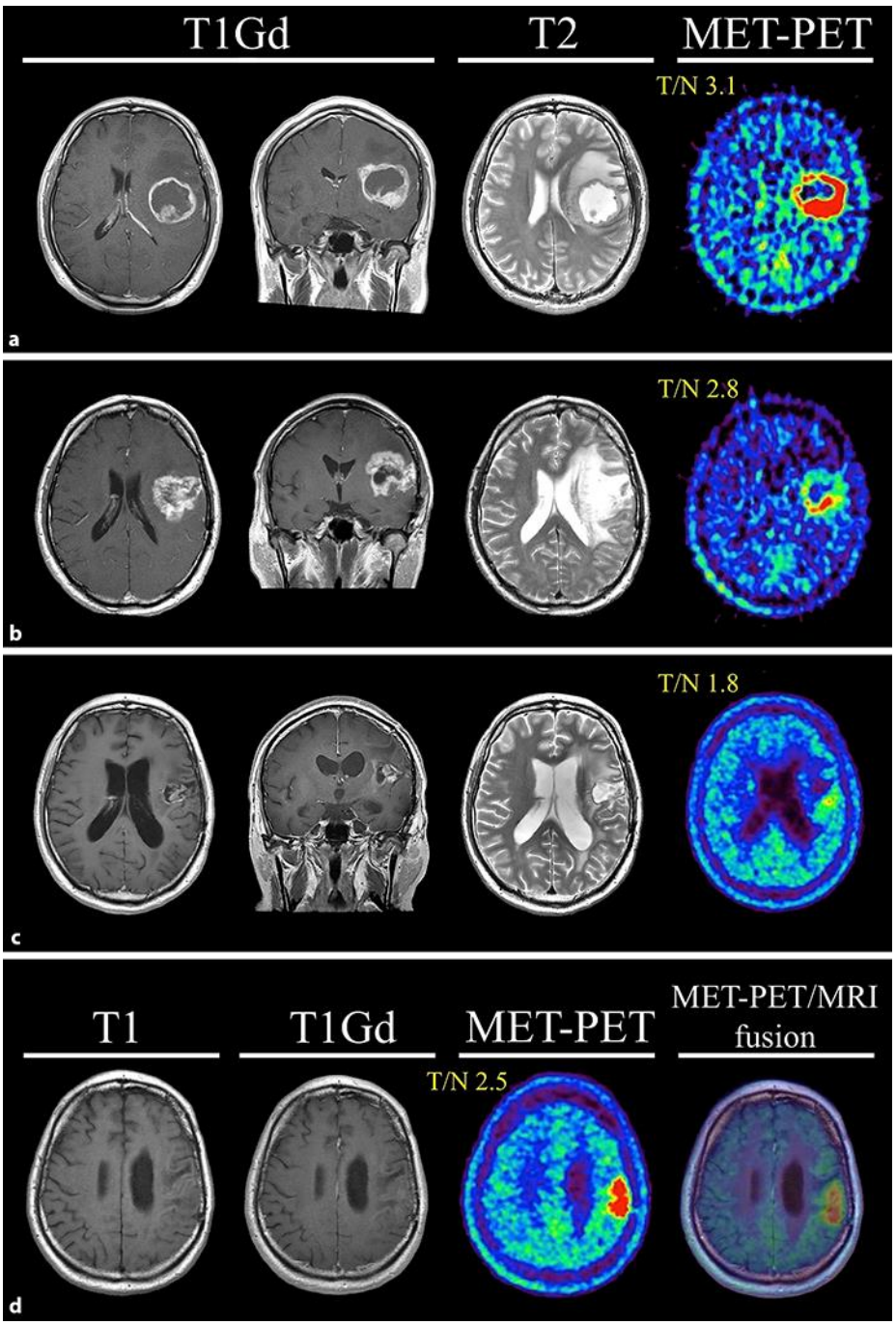

Fig. 1. Serial magnetic resonance (MR) and ^{11}C-methionine positron emission tomography (MET-PET) images. **a** Primary images of the tumor. Axial and coronal Gd-enhanced T1-weighted MRI shows a left frontal lobe tumor with ring enhancement. A strong perifocal edema can be seen on the T2-weighted image. High MET uptake on PET corresponds to the enhanced lesion. The ratio of the standardized uptake value to the contralateral normal tissue (T/N ratio) was 3.1. **b** Gd-enhanced T1-weighted MRI and MET-PET reveal tumor recurrence (T/N ratio: 2.8), and T2-weighted MRI shows deterioration of the edema after radiotherapy plus concomitant and adjuvant temozolomide therapy. **c** Complete remission, as assessed by the Response Assessment in Neuro-Oncology (RANO) criteria, demonstrated after administration of bevacizumab (BEV) for 2 months, and MET uptake almost disappeared after initiation of BEV (T/N ratio: 1.8). **d** T1-weighted MR, Gd-enhanced T1-weighted MR, MET-PET, and MET-PET/MR fusion images 17 months after initiation of BEV. No enhanced lesion can be seen on Gd-enhanced MRI, but MET-PET detected non-enhanced tumor recurrence (T/N ratio: 2.5).

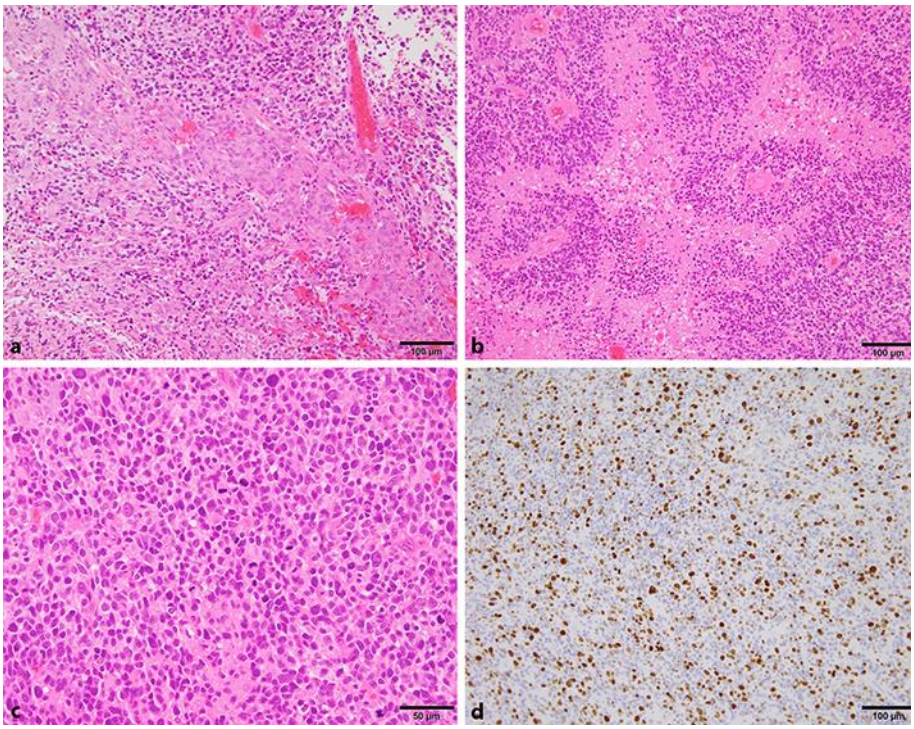

Fig. 2. Histopathology of the tumor. Microvascular proliferation (**a**), coagulative necrosis, pseudopalisading (**b**), anaplasticity, nuclear atypia, and cellular pleomorphism (**c**) were observed with HE staining, and they confirmed the diagnosis of glioblastoma. Immunohistochemical staining for MIB-1 demonstrated a MIB-1/Ki-67 labeling index of 38.6% (**d**).

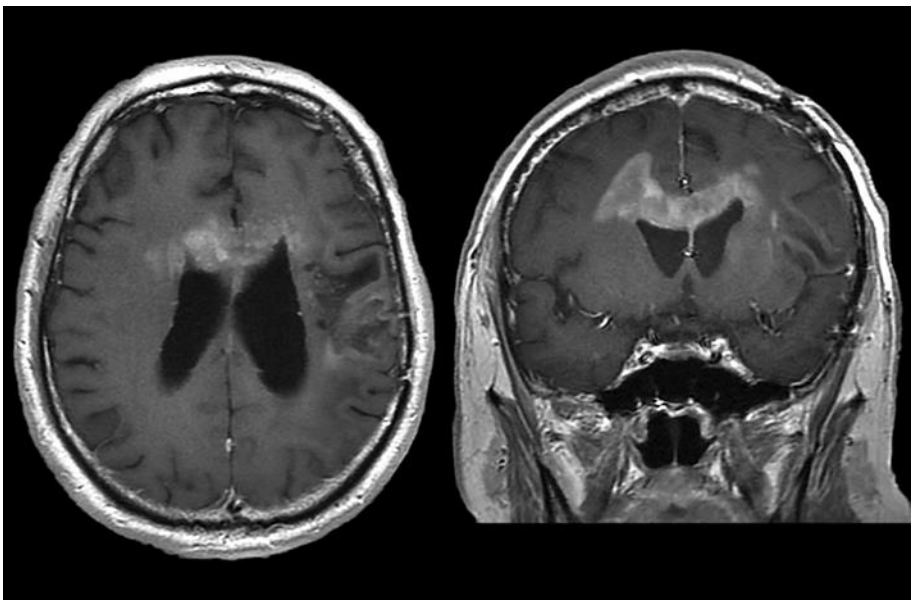

Fig. 3. Gd-enhanced T1-weighted magnetic resonance (MR) images obtained after 22 months of continuous bevacizumab administration. Rapid growth of an enhanced tumor lesion on MRI, including contralateral invasion through the corpus callosum, appeared after 22 months of continuous bevacizumab administration.