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Hyperperfusion and Hypermetabolism in Brain Radiation Necrosis with Epileptic Activity

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We report a case of high uptake of ¹¹C-methionine (MET), ¹⁸F-FDG (FDG) and ²⁰¹Tl-Cl (TI) in brain radiation necrosis. Twenty-one years previously, the patient had undergone surgery and radiation therapy consisting of 60-Gy for ependymoma in the anterior horn of the right lateral ventricle. The clinical features consisting of frequent seizures of the left face and arm suddenly appeared 2 wk before admission. MRI depicted a T1- and T2-prolonged lesion in the right frontal lobe. Abnormally high uptake in this area demonstrated by MET-PET, FDG-PET, TI-SPECT or HMPAO-SPECT suggested the presence of a recurrent tumor. A craniotomy was then performed and an intraoperative electrocorticogram showed continuous epileptic spikes in the lesion. The epileptic foci were resected and the histological features of the lesion were consistent with radiation necrosis. After surgery, the seizures disappeared and the postoperative examinations with MET-PET, FDG-PET, TI-SPECT and HMPAO-SPECT no longer showed abnormally high uptake. Hypermetabolism and hyperperfusion related to epileptic fits are therefore thought to result in high uptake of MET, FDG and TI in radiation necrosis.

Key Words: radiation necrosis; thallium-201-chloride; carbon-11-methionine; fluorine-18-FDG; SPECT; PET

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Brain radiation necrosis is one of the late complications of radiotherapy for tumors of the central nervous system. The recurrence of clinical symptoms suggesting a recurrence of the tumor may also represent radiation necrosis of the brain. Distinguishing between radiation necrosis and tumor recurrence may be difficult with either CT (1) or MRI (2) because the information provided by these modalities are based on structural changes and is not specific to any histological lesion type. PET has been used to evaluate the metabolic activity of tumors by using ¹¹C-L-methionine (MET) and [¹⁸F]fluorodeoxyglucose (FDG). Both MET-PET and FDG-PET have been reported to be useful in detecting primary brain tumors (3,4) as well as differentiating recurrent tumors from radiation necrosis after radiotherapy (5,6). SPECT with ²⁰¹Tl chloride (TI) also has been reported to be useful in differentiating recurrent tumors from brain radiation necrosis after treatment (7,8). We, how-

ever, recently encountered a case of radiation necrosis in which the patient demonstrated high uptake of MET, FDG and TI.

CASE REPORT

A 37-yr-old woman was admitted to our hospital with frequent seizures of the left face and arm for 2 wk. Twenty-one years earlier, the patient had undergone surgical resection of the ependymoma in the anterior horn of the right lateral ventricle through a frontal transcortical approach. Postoperative radiation therapy was performed with 30 Gy/15 Fraction (F) of whole-brain irradiation (14 × 16 cm) with additional local regional irradiation (6 × 9 cm) of 30 Gy/15 F by using ⁶⁰Co gamma rays, both irradiations were weighed on the right side by 2:1, followed by whole-spine irradiation with 30 Gy/15 F to prevent spinal dissemination. The patient was free of any clinical symptoms for 21 yr after the above therapy and suddenly developed seizures of the left face and arm 2 wk before admission. Her seizures began with an abnormal sensation in her left arm, followed by rapid grimace like contractions of the lower half of the left face and jerking pronating-supinating movements of the forearm. Postictally, mild weakness in these areas occurred for about 1 hr. Despite treatment with 400 mg of sodium valproate and 200 mg of zonisamide, she developed frequent seizures several times a day during her hospitalization.

MRI (T1-weighted spin-echo images were obtained with sequences of 500/18/1 (TR/TE/excitations). T2-weighted fast spin-echo images were obtained with 2500/110/1) demonstrated a T1- and T2-prolonged lesion in the right frontal lobe just posterior to the surgical defect of the previous corticotomy (Fig. 1A). The T1-weighted MR image after the administration of Gd-DTPA (0.1 mmol/kg) demonstrated patchy enhancements on the lesion (Fig. 1B).

MET-PET images (acquired 15 postadministration of 370 MBq MET) demonstrated widespread, high uptake in the right frontal lobe (Fig. 2A). The most intense uptake was observed in the area just posterior to the surgical defect, which was 3.2 times that of the contralateral frontal cortex. FDG-PET images (acquired 20 min after administration of 185 MBq FDG) also demonstrated high uptake in the area (Fig 2B), which was 1.2 times that of the contralateral frontal cortex. The cerebral blood flow increased in the right frontal lobe and was 1.7 times that of the contralateral frontal cortex (Fig. 2C). The TI-SPECT images (obtained 15 min after administration of 148 MBq TI) also demonstrated an abnor-

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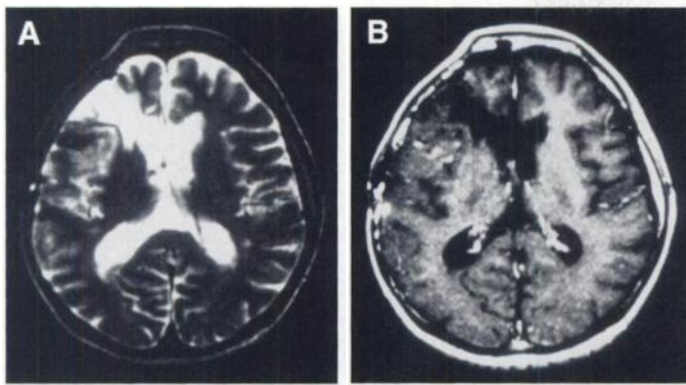


FIGURE 1. (A) T2-weighted MR image (TR2500/TE110) demonstrates a T2-prolonged lesion posterior to the surgical defect in the right frontal lobe. (B) After administration of Gd-DTPA, the T1-weighted MR image (TR500/TE18) demonstrates patchy enhancements on the lesion.

mally high uptake in this area (Fig. 2D), which was 6.4 times that of the contralateral region. No clinically apparent seizures were observed during either examination.

Tumor recurrence was thus suggested by both the PET and the SPECT studies. Therefore, right fronto-temporo-parietal craniotomy was performed. Although the right inferior and middle frontal gyli posterior to the previous corticotomy were slightly swollen, no tumorous lesions were observed. An intraoperative electrocorticogram (ECoG) with subdural grid electrodes showed continuously

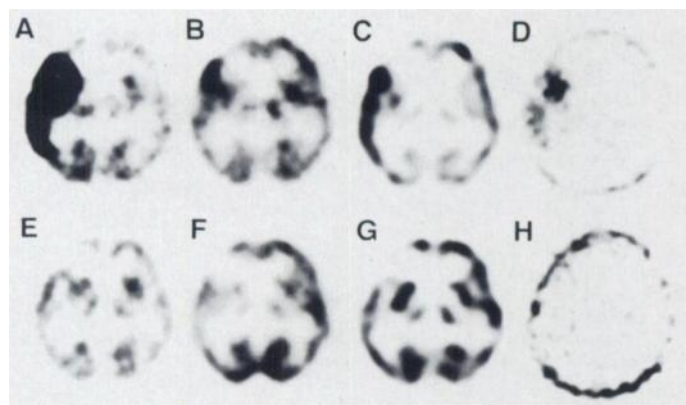


FIGURE 2. Preoperative examinations demonstrate high uptake of MET (A), FDG (B), HMPAO (C) and Tl (D) in the right frontal lobe. In all examinations, the most intense uptake is observed at the area just posterior to the surgical defect. Postoperative examinations, 2 mo after surgery, demonstrate a new surgical defect in the right frontal lobe without any abnormally high uptake by MET-PET (E), FDG-PET (F) or HMPAO-SPECT (G). Tl-SPECT demonstrates no abnormal uptake (H).

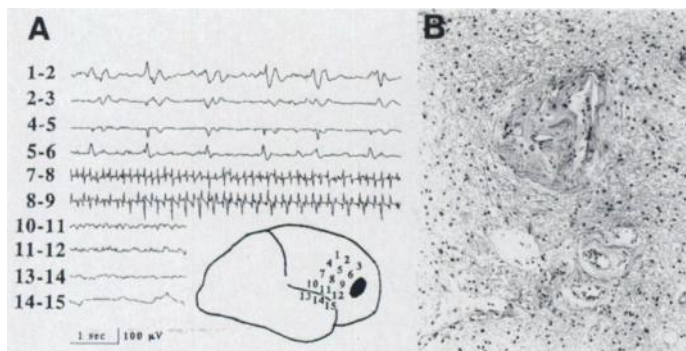


FIGURE 3. (A) Intraoperative electrocorticogram shows continuously discharging spikes along with frequent spikes and sharp waves on the frontal lobe posterior to the surgical defect (indicated by a closed circle). These paroxysmal activities demonstrate phase reversals at electrodes 2, 5 and 8. (B) Histological examination demonstrates the rarefaction of white matter and the vessels with a thick hyalinized wall (H&E, 114 \times).

discharging epileptic spikes on the cortex posterior to the surgical defect where the highest uptake was demonstrated on MET-PET, FDG-PET, HMPAO-SPECT and Tl-SPECT (Fig. 3A). Surgical resection of the epileptic foci measuring 3 \times 3 \times 2 cm was performed to control her seizures and for biopsy purposes. After the resection, intraoperative ECoG did not demonstrate any sharp waves.

After surgery, she became free from seizures. A microscopic examination demonstrated scattering necrotic foci accompanied by a few foam cells around vessels with a thick hyalinized wall (Fig. 3B). These histological features were consistent with radiation necrosis but no evidence of tumor recurrence was found. Two months after surgery, follow-up examinations were performed. MET-PET, FDG-PET and HMPAO-SPECT demonstrated a surgical defect in the right frontal region without any abnormally high uptake (Fig 2E, 2F, 2G). In addition, Tl-SPECT did not show any abnormal uptake (Fig 2H).

DISCUSSION

In our patient, the clinical symptoms of radiation necrosis developed after a 21-yr interval. Although 75% of radiation necrosis cases are apparent within 3 yr, the latency period between the end of irradiation and the occurrence of clinical symptoms varies from months to years (9,10). Irradiation induces slow but progressive vascular changes consisting of hyalinization, fibrosis and mineralization of the vessel walls in the irradiated field. In addition to the vascular changes, some hemodynamic factors such as the alteration of the intracranial pressure or the blood pressure are thought to induce ischemic lesions mainly in the white matter which are consistent with delayed type radiation necrosis (10). The variation in the latency period of radiation necrosis is thus thought to be influenced by a combination of the degree of vascular changes and hemodynamic changes.

Both MET-PET and FDG-PET have been used to evaluate the metabolic activity of brain tumors. MET is considered useful for determining tumor boundaries (11), while FDG is useful for evaluating the degree of malignancy (4). Both MET and FDG may be useful in differentiating recurrent tumors from radiation injury (5,12-17). Tl-SPECT has also been reported to be useful for detecting gliomas (18-21) as well as differentiating recurrent tumors from radiation necrosis (7,8,17). In previous reports, abnormal uptake of MET (12), FDG (14,17) and Tl (7,8,17) in radiation necrosis were observed, although their degrees of uptake were not higher than those in recurrent tumors. However, the reason for such uptake was not clearly explained. Recently, high uptake of both MET and FDG was reported in non-neoplastic tissue, such as that seen in brain abscesses (22,23), brain hematomas (24) and, for MET, in cerebral ischemia (25). The blood-brain barrier (BBB) disruption is thought to result in leakage of these radiopharmaceuticals to the extracellular space and enables increased uptake in the cells (26), but the BBB disruption alone does not necessarily increase the uptake (19). In addition to the BBB disruption, some modifications of the transport mechanism, such as the gliotic reaction, inflammatory changes or hyperperfusion, may be responsible for the increased uptake of MET, FDG and Tl in nontumorous lesions.

The clinical features of our patient consisted of frequent seizures. The first symptoms of the radiation necrosis are mostly seizures, predominantly of a focal character, though the exact mechanism of epileptogenicity in radiation necrosis has not yet been clarified (10). In our patient, no clinical seizures were observed during either examination. Although no EEG monitoring was performed during either examination, the con-

tinuously discharging epileptic spikes demonstrated by intraoperative ECoG suggested the presence of subclinical seizures. A subclinical seizure is thought to be responsible for hyperperfusion (27) and hypermetabolism (28). The most intense uptake of these radiopharmaceuticals as observed in the frontal lobe just posterior to the surgical defect where the epileptic spikes were demonstrated by intraoperative ECoG. The hyperperfusion demonstrated by HMPAO-SPECT may have been induced by the subclinical epileptic activities. The high uptake of FDG may result from hypermetabolism which can be also induced by subclinical epileptic activities. The high uptake of both MET and TI is considered to be the result of an alteration in the transport mechanism due to the hyperperfusion and to the BBB disruption (25,29,30). Hypermetabolism may also play an important role in the high uptake of both MET and TI.

Postoperative examinations demonstrated no abnormal uptake of MET, FDG, TI or HMPAO. Although the localized area of the epileptic focus in the right frontal lobe was surgically removed, the high uptake in the posterior frontal lobe, adjacent to the epileptic foci, disappeared. It has been reported that the spread of epileptic activity to adjacent areas was demonstrated by both hypermetabolism (29) and hyperperfusion (31). The disappearance of the high uptake in the frontal lobe, posterior to the resected epileptic foci, strongly suggests that such high uptake was the result of the spread of epileptic activity.

CONCLUSION

Abnormally high uptake of MET, FDG and TI could not differentiate brain radiation necrosis from recurrent brain tumors when epileptic activity exists on the lesion.

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