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Increased Uptake of ^{99m}Tc-HMPAO in Necrotic Brain Tumors

^{99m}Tc complex of hexamethylpropylene amine oxime (^{99m}Tc-HMPAO), which has been used as a tracer for regional cerebral blood flow (rCBF), has been shown to localize in primary brain tumors with wide spectrum of its uptake. The causes of the wide spectrum of tumor uptake, however, has not been understood in detail. We performed autoradiographic study with this agent to get further knowledge about HMPAO distribution in 10 cases of transplanted rat gliomas. Eight cases of rat gliomas without tumor necrosis, showed decreased uptake of ^{99m}Tc-HMPAO in the autoradiography (average tumor/normal (T/N) uptake ratio: 0.75, range: 0.40-0.90). On the other hand, two cases with tumor necrosis revealed increased uptakes of this agent in central necrotic area. T/N uptake ratios of these two cases were 1.23 and 1.42, respectively. In addition, three patients with histologically proven glioblastoma with tumor necrosis were studied after administration of 20mCi ^{99m}Tc-HMPAO. Two out of three patients showed higher uptake of ^{99m}Tc-HMPAO in tumor necrotic area than the contralateral area. Our findings suggest that the necrotic area of brain tumor may retain ^{99m}Tc-HMPAO and causes an increased uptake.

Key Words : *Technitium Tc 99m exametazime, HMPAO; Glioma; Necrosis, tumor*

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INTRODUCTION

The neutral and lipophilic ^{99m}Tc complex of hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) is a blood-flow tracer that crosses the normal blood-brain-barrier and exhibits high first pass extraction (1). Preliminary investigations with this agent indicate that its distribution in the brain of animals (2) and human (3) is proportional to blood flow. The brain single photon emission computed tomography (SPECT) using ^{99m}Tc-HMPAO has been extensively used to evaluate regional cerebral blood flow (rCBF) in cerebrovascular disorders. In addition, this study may be useful in predicting the effects of blood flow dependent therapies in gliomas like chemotherapy and radiotherapy (4). However, controversial observations were reported on the uptake behavior of this agent in brain tumor, especially in gliomas. As in the ^{99m}Tc-HMPAO SPECT study by Lindegaard et al., HMPAO uptake in tumor was significantly lower than in the corresponding region of the contralateral normal brain in 10 of 12 patients with gliomas (5). Nevertheless, Babich et al. (4) and Irvine et al. (6) described a greater variation of areas with marked increased tracer deposit as well as photopenic ones. Langen group reported that the uptake of HMPAO by gliomas showed a wide range of values without significant differences between malignant and benign gliomas (7). In the previous reported our series of ^{99m}Tc-HMPAO SPECT study, 13 cases out of 19 cases of glioma patients showed decreased uptake and 6 cases revealed increased uptake in tumors (8). Taken together, HMPAO uptake in gliomas seems to be variable, but it is generally lower than the uptake in normal brains. Another drawback of perfusion estimation is that a differentiation between viable tumor tissue and variable amount of necrotic tissue or edema is not possible (9). To date some controversy surrounds the precise mechanism of its uptake and the finding of HMPAO in gliomas.

We therefore underwent this study to get further knowledge about HMPAO distribution in gliomas using the transplanted rat glioma model. In addition, three cases of glioblastoma with tumor necrosis were studied using HMPAO SPECT imaging.

MATERIALS AND METHODS

^{99m}Tc-HMPAO uptake in rat brain tumor

Ten female Fischer rats, each weight in 250 g to 300 g, were implanted with tumor cells from 9 L gliosarcoma cell line or C6 glioblastoma cell line. Both cell lines were grown in RPMI medium with 10% fetal calf serum.

Tumor cells (5×10^5 in 10 μl solution) were injected into the right cerebral hemisphere of the rats stereotactically. When they began to demonstrate neurological signs, such as hemiparesis, usually 15 days after tumor inoculation, 2 mCi of ^{99m}Tc-HMPAO was injected into the rat through the tail veins. Four hours after injection, the rats were sacrificed to remove the brains. Thirty-micrometer thickness whole brain frozen section slides were made in order to perform autoradiography and pathological examination. The slides were exposed to X-ray film (Fuji Super HR-G) for 12 to 24 hours. The autoradiographic images were compared with pathologic findings. In addition, we took tumor tissues and contralateral normal brains to seek tumor/normal brain (T/N) uptake ratios using gamma counter (Aloka, Model; TDC-5, well type).

^{99m}Tc-HMPAO uptake in patients with glioblastoma and tumor necrosis

In order to determine the pattern of HMPAO uptake in tumor necrosis of human glioblastomas, ^{99m}Tc-HMPAO SPECT was performed in three patients with glioblastoma. These patients were histologically confirmed to have central necrosis. ^{99m}Tc-HMPAO SPECT images were obtained on a single-head gamma camera equipped with low-energy, general purpose, parallel-hole collimators (TRIAD, TRIONIX, Ohio, USA). SPECT imaging was performed 20 min and 3 hr after administration of 20 mCi of ^{99m}Tc-HMPAO.

RESULTS

In all of 10 rats glioma cell line implanted, grossly visible tumor masses were found in brain. There was no tumor necrosis in 5 cases of 9 L gliosarcoma implanted group, however, 2 out of 5 cases of C6 implanted group

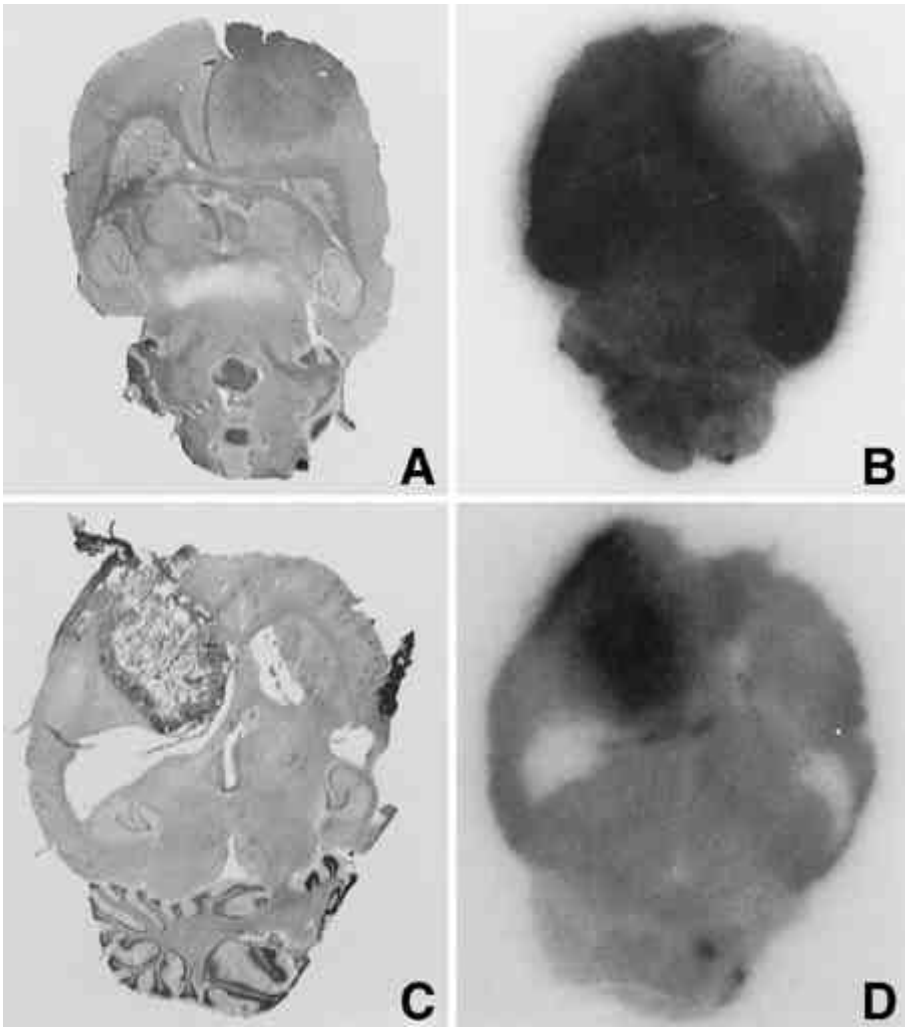

Fig. 1. ^{99m}Tc-HMPAO autoradiography of rats with C6 glioblastoma. The tumor without necrosis show decreased uptake of ^{99m}Tc-HMPAO (A and B). In contrast, tumor necrotic region reveals high uptake of this agent (C and D).

Table 1. ^{99m}Tc-HMPAO uptake in rat brain and glioma

	Uptake of normal (cpm/g)	Uptake of tumor (cpm/g)	T/N ratio
Cell line			
9L No. 1	4,528,214	3,855,574	0.85
No. 2	9,447,655	3,768,107	0.40
No. 3	15,141,715	9,304,050	0.61
No. 4	4,021,379	2,790,000	0.69
No. 5	3,286,744	2,779,431	0.85
C6 No. 1	5,236,429	4,252,069	0.81
No. 2	4,342,500	3,904,762	0.90
No. 3	21,718,626	19,541,306	0.90
No. 4*	2,078,740	2,562,000	1.23
No. 5*	1,449,269	2,061,040	1.42
Average			1.05

* C6 No. 4 and 5 have intratumoral necrosis.

showed tumor necrosis (Fig. 1). On microscopic examination, both groups showed malignant feature such as hypercellularity, mitosis and invasiveness. C6 cell line implanted group showed tumor necrosis which is one of the important histological findings of human glioblastoma but there were no hemorrhages.

All of eight cases without tumor necrosis showed decreased uptake of ^{99m}Tc-HMPAO in the autoradiography (average T/N uptake ratio, 0.75). On the other hand, two cases with the tumor necrosis revealed increased uptakes of this agent in central necrotic area. Furthermore, the uptakes in central necrotic area were higher than those in marginal viable tumor area (Fig. 1). T/N uptake ratios of these two cases were 1.23 and 1.42 (Table 1).

^{99m}Tc-HMPAO SPECT analysis demonstrated higher uptake of ^{99m}Tc-HMPAO in tumor necrotic area than the contralateral area in 2 out of 3 glioblastoma patients (Fig. 2).

DISCUSSION

To date, there is a consensus that homogenous low grade gliomas show decreased uptakes in HMPAO-SPECT, but heterogenous malignant gliomas have very

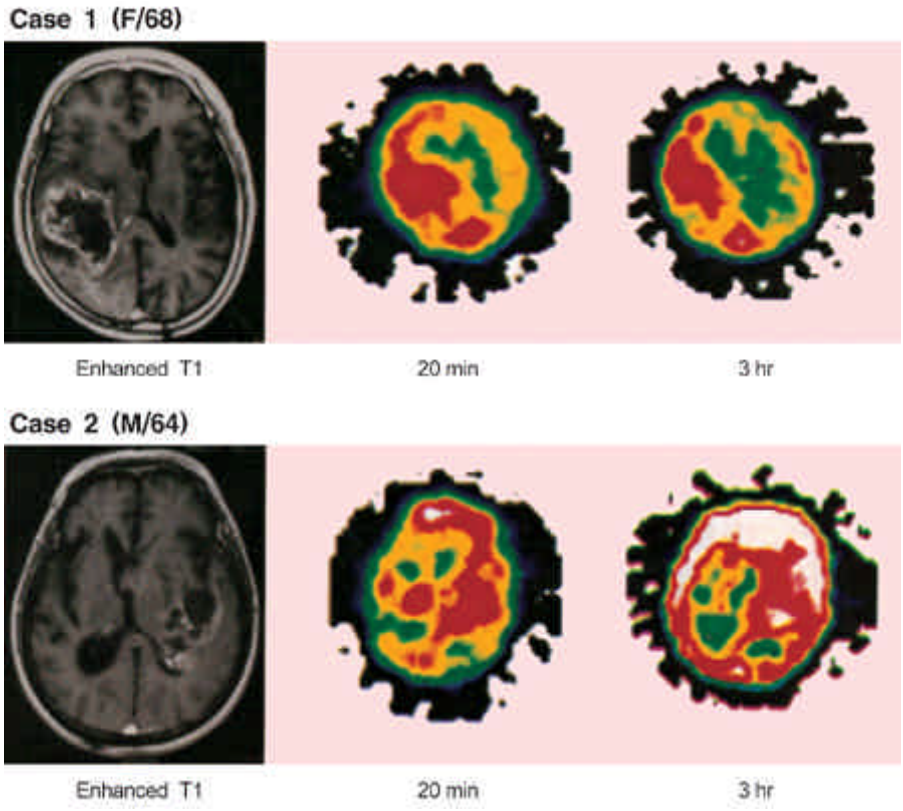

Fig. 2. ^{99m}Tc-HMPAO SPECT and MRI images.
Case 1, F/68: Glioblastoma with central necrosis in right temporal lobe. Contrast enhanced T1-WI reveals no enhancement in central necrosis. SPECT images obtained 20 min and 3 hr after administration of 20 mCi of ^{99m}Tc-HMPAO shows a high uptake in right temporal area.
Case 2, M/64: Glioblastoma with central necrosis in left temporal lobe. Contrast enhanced T1-WI shows no enhancement in central area. SPECT image shows a high uptake in left temporal area.

often both high and low uptake zones in SPECT images, due to central necrosis and perifocal edema (10). The cystic and necrotic portions have decreased rCBF, and the uptake of HMPAO in these portions should be lower than the surrounding normal brain (6). Langen et al. (7) studied cerebral uptake of ^{99m}Tc-HMPAO in 66 patients with various types of brain tumors. They reported that the uptake of HMPAO by gliomas showed a wide range of values.

Furthermore, it is possible that local flow in gliomas was underestimated due to pathologic intrinsic vasculature and variable amounts of arteriovenous shunting (5). Biersack et al. (9) also suggested that HMPAO brain SPECT in tumorous lesions seems to be only of value in the follow-up of patients under treatment.

In our study, rat gliomas consisted of homogenous cellular component and numerous tumor vessels microscopically, that imply increased rCBF in rat gliomas. Nevertheless, rat gliomas showed decreased HMPAO uptakes. This result is in agreement with previous reports on the decreased uptake of HMPAO in human gliomas. Our findings therefore support the theory that ^{99m}Tc-HMPAO SPECT study may underestimates regional blood flow at high flow regions.

Interestingly, unexpected increased uptakes of HMPAO were observed in tumor necrotic portions in this study. There were no inflammatory cells and hemorrhage in necrotic area microscopically. In contrast, viable tumor tissue surrounding necrotic region showed low uptake of this agent. These findings contrast with previous reports that described necrotic glioma as area of decreased uptake of HMPAO.

In fact, the rat glioma model we used, is not exactly same as human gliomas. To confirm increase uptake of HMPAO in necrotic area in human glioblastoma, we did ^{99m}Tc-HMPAO SPECT in three cases of glioblastoma carrying central necrotic portion. Two out of 3 cases, we also observed increase uptakes of HMPAO in central necrotic areas. Even if sample size is small and further works are necessary to determine the extent to which pathological processes in gliomas affect the uptake kinetics of HMPAO, our results indicate that a certain stage of tumor necrosis may show increased HMPAO uptake.

HMPAO has been used for many years with the assumption that this molecule passes the blood brain barrier through cell membranes and is retained after intracellular conversion to a hydrophilic form. This intracellular conversion of HMPAO has been related to the glutathione content (10). However, Jacquier-Salin et al. (11) reported that overall intracellular retention of HMPAO is more dependent upon the oxido-reductive state of the tissue than the intracellular glutathione content. Thus, the high uptake of HMPAO in brain tumor necrosis is more likely due to the alteration of oxido-reductive state, such as hypoxic state and/or pH change, than the intracellular glutathione content.

According to our results, HMPAO uptake may not exactly correlate with rCBF in certain cases of gliomas and the severe disruption of blood-brain-barrier or the alteration of oxido-reductive state may be possible mechanisms of increased uptake of HMPAO in necrotic regions. Also we think that the results for rCBF in brain gliomas, found by HMPAO SPECT, must be interpreted with caution.

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