Carbon-11-Methionine PET Evaluation of Intracerebral Hematoma: Distinguishing Neoplastic from Non-Neoplastic Hematoma

Toshihide Ogawa, Jun Hatazawa, Atsushi Inugami, Matsutaro Murakami, Hideaki Fujita, Eku Shimosegawa, Kyo Noguchi, Toshio Okudera, Iwao Kanno, Kazuo Uemura, Hiromu Hadeishi and Toshio Sasajima

Departments of Radiology and Nuclear Medicine and Surgical Neurology, Research Institute of Brain and Blood Vessels, Akita, Japan; Department of Neurosurgical Service, Akita University School of Medicine, Akita, Japan

We evaluated whether PET with L-methyl-^{11}C-methionine (^{11}C-methionine) was clinically useful in distinguishing neoplastic from non-neoplastic intracerebral hematoma. **Methods:** We examined eight patients with neoplastic (n = 4) or non-neoplastic (n = 4) intracerebral hematomas between 5 and 68 days after the bleeding episode using PET with ^{11}C-methionine (Met-PET). **Results:** Carbon-11-methionine accumulated in the area surrounding the hematoma in both groups, except in one patient with an acute hypertensive hematoma. Between 22 and 45 days after the ictus, non-neoplastic hematomas showed increased ^{11}C-methionine accumulation largely in accordance with the contrast-enhanced areas on CT or MR images; whereas between 14 and 68 days after bleeding, neoplastic hematomas showed increased ^{11}C-methionine accumulation that extended beyond the contrast-enhanced areas on CT or MR images. The intensity of ^{11}C-methionine accumulation in tumor tissue was greater than that in non-neoplastic hematomas. **Conclusion:** Preliminary results suggest that Met-PET can distinguish neoplastic from non-neoplastic hematomas on the basis of differences in lesion extent compared with CT or MR findings.

Key Words: positron emission tomography; carbon-11-methionine; intracerebral hematoma; brain tumor

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Two percent to 14% of spontaneous intracerebral hemorrhages are secondary to tumors (*1–3*). Although their incidence varies depending on the series, neoplastic hemorrhages are not rare. In treating patients with intracerebral hemorrhage, it is thus important to accurately diagnose the etiology. Although CT and MRI can provide useful information for distinguishing hemorrhagic intracranial neoplasms from non-neoplastic hematomas (*4–6*), differentiation is sometimes difficult because of considerable overlap between the imaging findings of these two types of lesions.

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For correspondence or reprints contact: T. Ogawa, MD, Department of Radiology and Nuclear Medicine, Research Institute of Brain and Blood Vessels-Akita, 6-10, Senshu-kubota-machi, Akita City, 010, Akita, Japan.

PET with L-methyl-^{11}C-methionine (^{11}C-methionine) has been shown to be clinically useful in evaluating patients with brain tumors (*7–10*), but its application to nontumorous lesions is still limited (*11–13*). To determine whether PET with ^{11}C-methionine (Met-PET) is helpful in distinguishing neoplastic from non-neoplastic hematomas, we used this method to evaluate eight patients with neoplastic or hypertensive hematoma.

MATERIALS AND METHODS

Patients

This study included four patients with neoplastic and four with non-neoplastic intracerebral hematoma (Table 1). In the former group, one patient (Patient 1) was examined with Met-PET 5 days after the bleeding episode and the other patients between 14 and 68 days after bleeding. Patient 2 underwent two examinations, at 14 and 50 days after bleeding.

In the non-neoplastic group, one patient (Patient 5) was examined 5 days after bleeding (acute stage of the hematoma) and the other patients between 22 and 45 days after bleeding (subacute and chronic stages of the hematoma). Patient 6 underwent two examinations, 22 and 45 days after the bleeding episode.

All patients with neoplastic hematoma were histologically confirmed to have anaplastic astrocytoma grade III or glioblastoma multiforme at surgery. One patient (Patient 8) with hypertensive hematoma had surgery after clinical deterioration, while the remaining three patients with non-neoplastic hematoma were treated conservatively. From clinical and neuroradiological data, these patients were diagnosed as having hypertensive intracerebral hematoma. One and a half to 2 years after the bleeding episode, their hematomas had resolved completely and changed to scar.

PET

PET was performed using a scanner with a spatial resolution of 4.5 mm FWHM in the image plane and a slice thickness of 9.5 mm FWHM. Fourteen axial images were obtained at 6.5-mm intervals (*14*). A dose of 370–1480 MBq (10–40 mCi) ^{11}C-methionine was injected intravenously into the cubital vein. Emission scans were begun 30 min after injection and were obtained for 12 min. CT or MRI was performed before and after injection of contrast medium (iopamidol 300 for CT, gadopentetate dimeglumine for MRI) in accordance with the PET plane on the same day of the PET study. The method of superimposing CT and MR images on the corre-

TABLE 1
Patient Data

Patient no.	Age	Sex	Hematoma location	Time of imaging after ictus (days)	Histology
1*	53	M	R temporal	5	Anaplastic astrocytoma grade III
2*	74	M	L frontal	14	Anaplastic astrocytoma grade III
				50	
3*	41	F	R temporal	68	Anaplastic astrocytoma grade III
4*	71	M	R temporal	39	Glioblastoma multiforme
5†	62	M	R cerebellum	5	—
6†	57	M	L parietal	22	—
				45	
7†	63	M	L putamen	23	—
8†	55	F	L frontal	32	—

*Patients with neoplastic hematoma.
†Patients with non-neoplastic hematoma.

sponding PET images has been previously described in detail (*15,16*).

Data Analysis

We evaluated the Met-PET data qualitatively and quantitatively. For qualitative analysis, we compared the extent of increased ^{11}C-methionine accumulation to the area of contrast enhancement on the CT or MR images by superimposing them on the corresponding PET image. For quantitative analysis, we evaluated the concentration of ^{11}C-methionine 36 min after injection using the mean pixel counts within a specified region of interest (ROI). We defined ROIs on the PET images within the area of increased ^{11}C-methionine accumulation surrounding the hematoma and within the contralateral posterior temporal gray matter as a representative area of structurally normal gray matter. In Patient 5, who had an acute hypertensive hematoma, increased ^{11}C-methionine accumulation around the hematoma was not detected, as we did not define any ROI in the area surrounding the hematoma. For this patient, who had a right cerebellar hematoma, we used the mean value of bilateral ROIs set in the posterior temporal gray matter. We calculated the differential absorption ratio (DAR) (*17*) of the lesions with increased ^{11}C-methionine accumulation and the contralateral posterior temporal gray matter as follows:

$$\text{DAR} = [(\text{pixel count/pixel volume})/(\text{injected radioisotope activity/body weight})] \times \text{calibration factor},$$

where the calibration factor is the ratio of PET camera counts to those obtained with a well counter.

We compared the data in this study with Met-PET results obtained from 50 patients with cerebral glioma (*10*).

RESULTS

Table 2 summarizes the data from CT, MRI and PET. In the group with hypertensive intracerebral hematoma, ^{11}C-methionine showed increased accumulation in part or most

TABLE 2
CT, MRI and Carbon-11-Methionine PET Findings

Patient no.	Contrast on CT/MRI	Met uptake	Area of contrast versus area of Met	DAR		
				Tumor or contrast lesion (A)	Gray matter (B)	A/B ratio
1	−	++	/	1.57	1.02	1.54
2	+	++	<	2.98	2.16	1.38
	+	++	<	3.64	2.44	1.49
3	+	++	<	4.73	1.28	3.70
4	+	++	<	4.23	1.72	2.46
	Mean ± s.d.			3.43 ± 1.23*	1.72 ± 0.59	2.11 ± 0.99
5	−	−	/	/	1.29	/
6	+	++	=	1.92	1.24	1.55
	+	++	=	2.02	1.28	1.58
7	+	+	=	1.42	1.27	1.12
8	+	+	>	2.18	1.81	1.20
	Mean ± s.d.			1.89 ± 0.33*	1.38 ± 0.24	1.36 ± 0.24

*Difference between DAR in neoplastic and non-neoplastic hematomas is statistically significant by Student's t-test ($p < 0.05$).
CE = contrast enhancement (− = negative, + = positive); Met = ^{11}C-methionine (− = none, + = uptake almost the same as in cortex, ++ = uptake greater than cortex); DAR = differential absorption ratio.

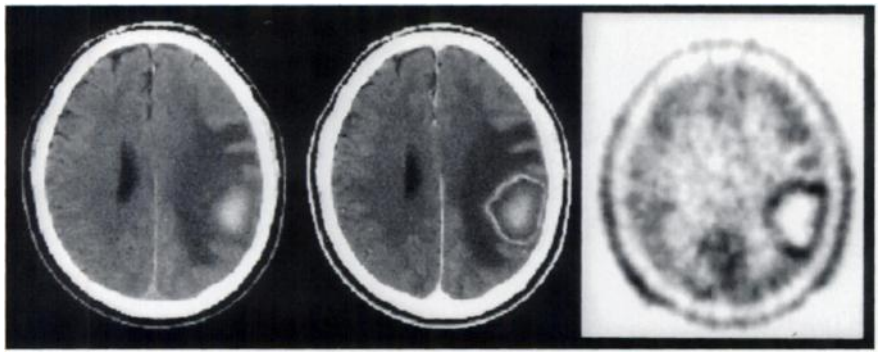

FIGURE 1. Patient 6. Left parietal subcortical hematoma 22 days after the bleeding episode. Noncontrast CT scan (left) shows a resolving hematoma with surrounding edema in the left parietal lobe. Contrast-enhanced CT scan (center) shows ring-like enhancement around the hematoma. Met-PET (right) shows increased accumulation of ^{11}C-methionine that is almost completely in accordance with the enhancing rim on the contrast-enhanced CT scan.

of the enhancing lesion surrounding the hematoma on CT or MR images from three patients. The accumulation of ^{11}C-methionine in the enhanced areas was almost the same as that in the contralateral gray matter in Patients 7 and 8. In Patient 6, who had two examinations, ^{11}C-methionine showed increased accumulation in accordance with the enhanced area on CT scans (Fig. 1). Accumulation was greater in the enhanced area than in the contralateral gray matter. In patient 5, studied in the acute stage, an enhancing rim surrounding the hematoma was not observed on MRI, while Met-PET showed a cold area in accordance with the hematoma (Fig. 2).

On the other hand, ^{11}C-methionine showed increased accumulation in the tumor tissue of Patient 1, who had an intratumoral hematoma studied in the acute stage, despite the lack of an enhancing lesion on CT (Fig. 3). In the other patients with neoplastic hematomas, Met-PET showed increased accumulation of ^{11}C-methionine extending beyond the enhanced area on CT scans or MR images (Figs. 4 and 5). Accumulations were higher in the tumor tissue than in the contralateral gray matter.

Quantitative analysis showed that the DAR of tumor tissue was significantly higher than that of the enhancing areas of the hypertensive hematomas ($p < 0.05$, Student's t-test). Moreover, the DAR of neoplastic hematoma was similar to that previously found in high-grade gliomas (3.51 ± 1.11, $n = 32$) (*10*). Conversely, the DAR of non-neoplastic hematoma was significantly lower than that of high-grade glioma ($p < 0.01$, Student's t-test). The ratio of tumor tissue to contralateral gray matter DAR values, however, was not significantly greater than that of enhancing hypertensive hematoma to contralateral gray matter DAR values. Finally, the contralateral gray matter DAR values were similar for neoplastic and hypertensive hematomas.

DISCUSSION

It has been reported that Met-PET can provide helpful information for the evaluation of brain tumors (*7–10*). In our study of cerebral glioma, Met-PET was clinically useful in assessing the extent of tumor invasion but not malignancy grade (*10*). Application, however, of this technique for nontumorous lesions, is still limited, despite a few observations that ^{11}C-methionine shows high accumulation in brain abscess and radiation necrosis sites (*12,13*). Recently, Dethy et al. (*18*) reported that high ^{11}C-methionine uptake was observed in the area around non-neoplastic hematomas 20–32 days after the bleeding episode in three patients. They concluded that Met-PET was not helpful in distinguishing between neoplastic and non-neoplastic intracerebral hemorrhage (*18*), but they had not compared the extent of increased ^{11}C-methionine accumulation with the contrast-enhanced area on the CT scans.

Tracer Distribution

In our study, ^{11}C-methionine showed increased accumulation in the region around the non-neoplastic hematomas 22–45 days after bleeding, but there was no accumulation in an acute non-neoplastic hematoma. The area of increased accumulation of ^{11}C-methionine corresponded well to part or most of the enhanced areas on the CT and MR images. For neoplastic hematomas, on the other hand, Met-PET showed increased accumulation of ^{11}C-methionine in a larger area beyond the enhanced lesions on CT MRI. These results agree with our previously reported findings

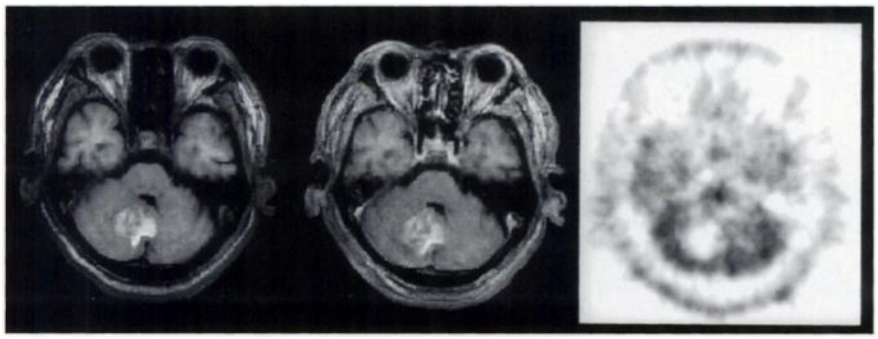

FIGURE 2. Patient 5. Right cerebellar hematoma 5 days after the bleeding episode. Noncontrast T1-weighted image (left) shows a hyperintense hematoma in the right cerebellar hemisphere extending to the vermis. Contrast-enhanced T1-weighted image (center) shows no enhancement around the hematoma after Gd-DTPA injection. Met-PET (right) shows a cold area corresponding to the hematoma.

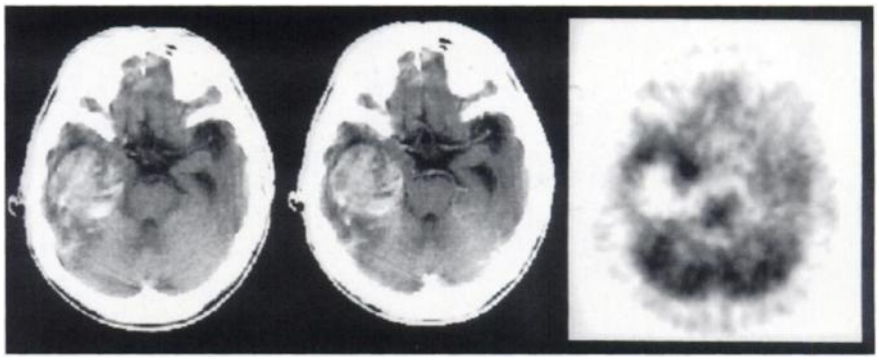

FIGURE 3. Patient 1. Neoplastic hematoma in the right temporal lobe 5 days after the bleeding episode. Noncontrast CT scan (left) shows a round hematoma in the right temporal lobe. No contrast enhancement around the hematoma is observed on the contrast-enhanced CT scan (center). Met-PET (right) shows increased accumulation of ^{11}C-methionine around the hematoma. Tumor tissue was confirmed around the hematoma at surgery.

that in most cases of cerebral glioma the area of increased ^{11}C-methionine accumulation is larger than that of the enhanced area on CT scans (*10*). Moreover, ^{11}C-methionine also showed high accumulation in acute neoplastic hematoma. Therefore, using Met-PET to observe differences in the extent of increased ^{11}C-methionine accumulation between neoplastic and non-neoplastic hematomas, we may be able to distinguish the two types of hematoma.

Quantitative Analysis

Although the neoplastic hematoma DAR was similar to that of high-grade glioma, it was impossible to differentiate neoplastic from non-neoplastic hematoma using DAR values because of overlap between the two groups. We previously reported that the rate of ^{11}C-methionine uptake in high-grade glioma is significantly higher than in low-grade glioma (*10*). Although this study comprised neoplastic hematomas caused by only high-grade glioma, the DAR of neoplastic hematoma caused by low-grade glioma is expected to be lower than that by high-grade glioma. Therefore, it will be difficult to differentiate neoplastic from non-neoplastic hematomas using the DAR values.

No valid model of protein synthesis rate calculation based on Met-PET has been described. Quantitative evaluation of ^{11}C-methionine accumulation kinetics requires sequential PET scanning, arterial blood sampling and measurement of ^{11}C-methionine in plasma, all of which is troublesome when many clinical Met-PET studies are needed. Hatazawa et al. stressed that corrections for plasma metabolites should be performed to obtain ^{11}C-methionine plasma activity as an input for quantitative assessment of in vivo amino acid metabolism in tumor tissue (*19*). On the other hand, they also showed that the uptake rate of ^{11}C-methionine in tumor tissue, assessed in their study by graphic analysis, was significantly correlated with the DAR value. Therefore, from a clinical perspective, DAR is a useful index of ^{11}C-methionine metabolism.

Mechanism of Carbon-11-Methionine Uptake

It is generally accepted that blood-brain barrier (BBB) breakdown is not a prerequisite for increased ^{11}C-methionine accumulation in tumor tissue. The mechanism of increased ^{11}C-methionine accumulation in malignant glioma with disruption of the BBB, however, is complex and remains unclear, although we suspect that the high metabolic demands of malignant tumors may be responsible. The ring of contrast enhancement seen on CT scans of resolving hematomas is generally thought to be related to two factors: proliferation of vascular granulation tissue and BBB breakdown (*20,21*). As the area of increased ^{11}C-methionine accumulation corresponded to that of enhancement on CT and MR images in our study, increased protein synthesis by inflammatory cells or proliferating glial cells in vascular granulation tissue may be responsible for increased ^{11}C-methionine accumulation in non-neoplastic hematomas in addition to BBB breakdown.

CONCLUSION

Our findings in this limited clinical series suggest that Met-PET may help to distinguish neoplastic from non-neoplastic hematomas on the basis of the extent of increased ^{11}C-methionine accumulation. Follow-up studies with Met-PET would be most useful. It is, however, also

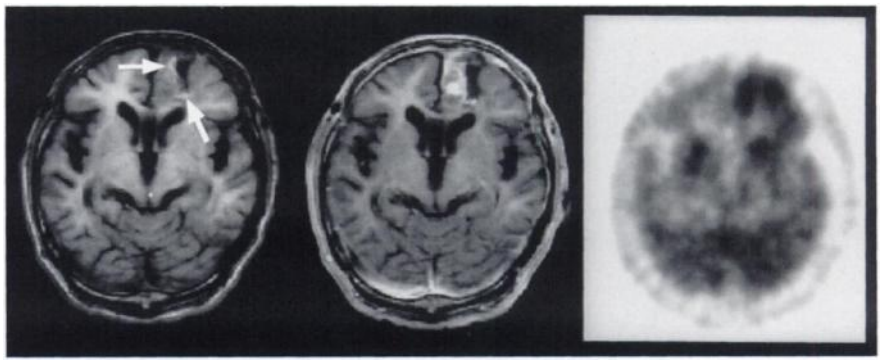

FIGURE 4. Patient 2. Neoplastic hematoma in the left frontal lobe 50 days after the bleeding episode. Noncontrast T1-weighted image (left) shows a hyperintense resolving hematoma (arrows) in the left medial frontal lobe. Contrast-enhanced T1-weighted image (center) reveals a heterogeneously enhanced lesion in the left medial frontal lobe. Met-PET (right) shows increased accumulation of ^{11}C-methionine extending from the left medial frontal to the lateral frontal lobe beyond the enhanced area on the CT scan.

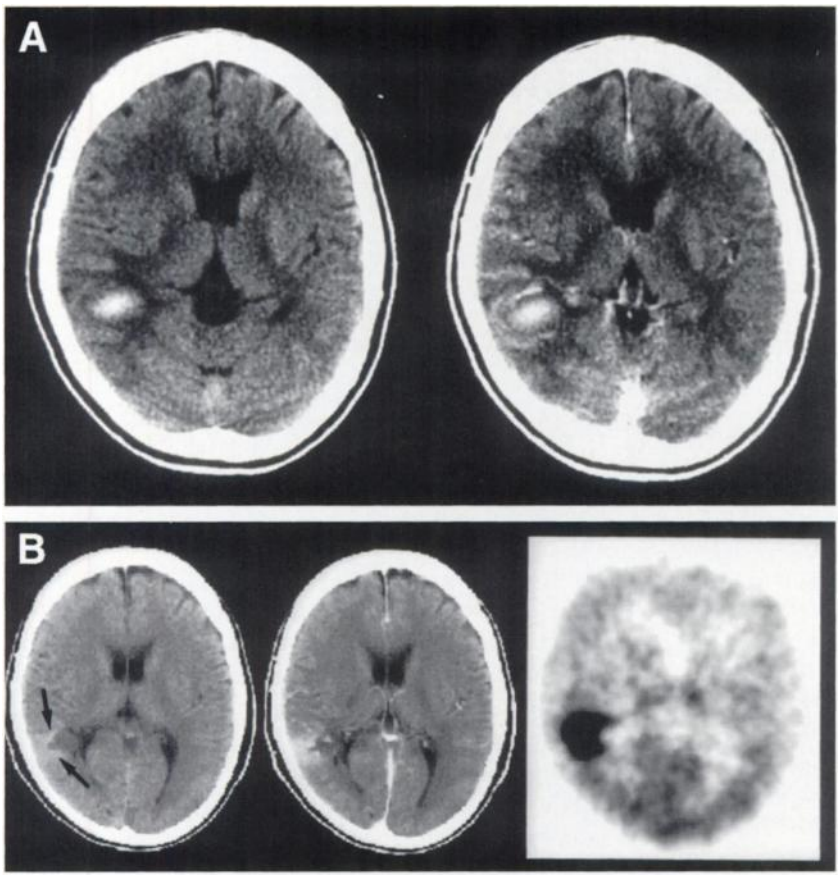

FIGURE 5. Neoplastic hematoma in the right temporal lobe in Patient 3. (A) Thirteen days after the bleeding episode. Noncontrast CT scan (left) shows a resolving hematoma in the right temporal lobe. Contrast-enhanced CT scan (right) shows contrast enhancement surrounding the hematoma. (B) Sixty-eight days after the bleeding episode. Noncontrast CT scan (left) shows a faint hyperdense area (arrows) around the right trigone of the lateral ventricle. The hyperdense area is markedly enhanced after infusion of contrast medium (center). Met-PET (right) shows high accumulation of ^{11}C-methionine extending beyond the enhanced area on the CT scan.

important to evaluate PET findings together with those obtained from CT and MRI. When increased ^{11}C-methionine accumulation extends beyond the enhanced area or occurs without an enhanced lesion on CT or MRI, a neoplastic origin should be suspected.

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