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Clinical Article

Diagnosis and treatment of progressive space-occupying radiation necrosis following stereotactic radiosurgery for brain metastasis: Value of proton magnetic resonance spectroscopy

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Summary

Background. There have been some reports that radiation necrosis can be controlled conservatively. There are rare cases showing progressive space-occupying radiation necrosis (PSORN). It is very difficult to control PSORN by conservative treatment. The purpose of this study was to evaluate the early diagnosis of those cases and the timing of surgery for patients with PSORN.

Method. We have experienced some cases where quality of life was improved by the removal of PSORN after stereotactic radiosurgery (SRS) for brain metastases. Therefore, we evaluated retrospectively the diagnosis and treatment of six cases of symptomatic PSORN at approximately 6–12 months after SRS for metastatic brain tumours.

Findings. In all six cases, on Magnetic Resonance Imaging with Gd contrast material (Gd-MRI), PSORN was revealed as a ring-like enhanced mass with large perifocal oedema coupled with the appearance of neurological deficit. Proton Magnetic Resonance Spectroscopy (^{1}H-MRS) enabled us to differentiate PSORN from recurrence of metastases in all six cases. Single Photon Emission Computed Tomography with thallium-201 chloride (^{201}TlCl-SPECT) enabled us to do this in four cases of the six. In four cases of the six, lesionectomy of the ring-like enhanced mass (PSORN) was performed, and in two of these cases the removal was performed within 4 weeks from the time when conservative treatment became ineffective, and the neurological deficit and perifocal oedema was improved as was the quality of life. However, in the other two patients who were left for more than 16 weeks, the deficit was gradually progressive. The two patients who did not receive lesionectomy were treated by conservative means with steroids and/or heparin and warfarin and they had progressive neurological symptoms.

Interpretation. Although, the number of patients is small in this study, and more data will be needed, it is recommended that lesionectomy is performed at an early stage, if possible, when conservative management has failed.

Keywords: Progressive space-occupying radiation necrosis (PSORN); lesionectomy; ^{1}H-MRS; stereotactic radiosurgery (SRS).

Introduction

The length of survival of patients with cancer is prolonged with improvement in local control. There is an increased incidence in the number of cerebral metastases [13]. Stereotactic radiosurgery (SRS) is widely used because it is less invasive than operation and achieves a high control rate [1, 27–29]. Although treated patients may develop radiation necrosis as a side effect of SRS, in many it can be controlled by conservative treatment. But progressive space-occupying radiation necrosis (PSORN) or radio-induced injury, occurs as a complication of SRS [30] and can be difficult to treat. The object of the present paper is to report our experience in the early diagnosis and management of PSORN.

Methods and materials

Patient population

The studies were performed according to the human research guidelines of the International Review Board of Asahikawa Medical College.

Informed consent was obtained from patients and their families. Twenty-five patients with metastatic brain tumour were treated with SRS at Asahikawa Medical College Hospital from October 1995 to July 1999. The group included 17 men and 8 women whose mean age at presentation was 62.3 years (range, 41–77 years). Twelve patients had lung cancer, 5 had renal cancer, 4 had rectal cancer, 2 had gastric cancer and 2 had breast cancer. Histological examination showed that 17 patients had adenocarcinoma, 6 had squamous cell carcinoma, and 2 had renal cell carcinoma. Stereotactic radiosurgery was performed by means of enhanced CT imaging with a CT localizing frame attached to the head-ring. The enhanced mass on the CT image was subjected to SRS with a volume of 0.52 to 14.13 ml being irradiated with 20 to 22 Gy to the 80% to 85% iso-dose line and 5 arcs using a linear accelerator. The volume of lesion was calculated from the diameter obtained on 3D-CT images obtained when planning treatment. Six patients later developed PSORN after a follow-up period ranging from 4 to 132 weeks (mean 31.5 weeks) after SRS.

Gd-enhanced MRI

MRI and ^{1}H-MRS studies were each performed on a whole body 1.5T Signa Horizon system with version 5.6 software (GE Medical System, Milwaukee, WI, U.S.A). The standard head coil was used in both MRI and MRS. In each patient T1-weighted SE images (TR/TE 600/15, matrix size 256×256, FOV 200×200 mm, 18 slices) were obtained immediately after intravenous injection of a contrast agent (0.1 mmol/kg Gd-dietylenetriamine pentaacetic acid dimeglumine [Gd-DTPA]). Slice thickness was 5 mm.

Localized ^{1}H-MRS

The axial spoiled gradient-echo (SPGR) imaging (TR/TE 100/4.2) using a 60° flip angle, a 256×192 matrix, a 200×200 mm FOV, and 21 slices preceded ^{1}H-MRS to define the volume of interest (VOI). The VOI was selected to include the enhancing mass present before stereotactic radiosurgery. The voxel size for MRS was 1.0 ml–15.3 ml to fit the tumour volume. The voxel sizes and the diameter of the tumours are shown in Table 1. The field homogeneity achieved in local shimming resulted in a water peak line width of 2 to 5 Hz. The size of VOI in the follow-up period was the same in each case. A chemical shift selective excitation (CHESS) pulse at the unwanted water resonance suppressed the water signal. The spectral data were transferred to a workstation (Sun SPARC classic workstation: Sun Microsystems Computer Corp. California, CA) for data processing. Typically, time domain data were zero filled to 4 K data points and an exponential line broadening (4 Hz) was done before Fourier transformation. A zero-order phase correction was applied to all spectra. Quantitative analysis of spectra was confined to choline-containing compounds (Cho) (chemical shift 3.2 ppm), creatine and phosphocreatine (Cr) (3.0 ppm), N-acetyl-aspartate (NAA) (2.0 ppm), lactate (Lac) (inverted doublet centered at 1.3 ppm with a coupling constant of 7 Hz), and lipid (Lip) signals (0.9 and 1.3 ppm). All signal intensity ratios were calculated from the spectra obtained with an echo time of 272 ms. The total examination time of the MRI and MRS was between 20 and 30 minutes.

The spectra were obtained using a point-resolved spectroscopic sequence (PRESS) with parameters of 2000/272 (TR/TE). The signal was collected using 2048 data points, spectral width of 2500 Hz, and 256 acquisitions (acquisition time, 8 min). The spectra were additionally obtained with an echo time of 136 ms, when a peak was observed at 1.3 ppm. Due to J modulation, the doublet signal of lactate is inverted (180° out of phase) relative to the singlets of Cho, Cr, and NAA at this TE [24]. The spectrum obtained with TE of 136 ms was utilized to evaluate the relative contributions of lactate and lipid signals to the peak at 1.3 ppm. That is, positive and negative peaks were interpreted as representing lipid-dominant (Lip) and lactate-dominant (Lac) signals, respectively.

^{201}TlCl-SPECT study

^{201}TlCl-SPECT was performed before treatment and at the time when recurrence of the tumour was suspected. After the intravenous injection of ^{201}TlCl (111 MBq), patients underwent SPECT imaging with the four-headed gamma camera system (SPECT 2000H, Hitachi Medical Corp., Tokyo, Japan). Data acquisition began 10 minutes after the administration of tracer and was continued for 20 minutes. Ninety projections with 360-degree rotation were collected with the low-energy high-resolution collimators (LEGP) and an energy window of 71 ± 14 KeV. Transaxial SPECT images were displayed with a slice thickness of 5 mm. The indices of ^{201}Tl uptake (^{201}Tl index) were defined as the ratio of the mean counts per pixel in the tumour portion to those in the normal contralateral parenchyma. The region of interest (ROI) was set around the region of maximum ^{201}Tl uptake with a threshold of 70%. The ROI of the normal contralateral parenchyma was more than 3 cm in diameter.

Diagnosis of PSORN

In the Gd-MR images, the effect of treatment was evaluated based on the change in size of the enhanced lesion or the enhanced effect. In ^{201}TlCl-SPECT studies, it has been reported that the positive predictive value of an L/N ratio of more than 2.5 for diagnosing recurrence is 83.3% and of ratios less than 2.5 for diagnosing necrosis is 100% [10]. Therefore, an L/N ratio of less than 2.5 in ^{201}TlCl-SPECT was defined as PSORN (not recurrence) in this study. In ^{1}H-MRS, PSORN was also evaluated based on a threshold level of Cho/Cr ratio. The positive predictive value of Cho/Cr ratios of more than 2.48 for diagnosing metastatic brain tumour and of Cho/Cr ratios less than 2.48 for identifying radiation necrosis were 88.9% (95%CI [confidence interval]:

Table 1. *The summary of 6 cases of radiation necrosis*

Case	Total dose SRS	^{1}H-MRS* Cho/Lip	^{1}H-MRS* Cho/Cr	Tl index* L/N ratio	Period for conservative	Periods until lesionectomy	Degree of removal	Outcome (Karnofsky scale)
1	20 Gy	0.26 (3.51)	1.63 (3.14)	1.95 (2.84)	16 w	4 w	total	90
2	20 Gy + 20 Gy	0.19 (2.46)	2.32 (3.62)	2.71 (3.82)	9 w	3 w	subtotal	90
3	22 Gy	0.20 (2.58)	1.21 (2.94)	1.94 (2.79)	12 w	16 w	total	30
4	22 Gy + focal 36 Gy	0.23 (2.92)	1.76 (3.24)	2.52 (1.72)	12 w	18 w	total	30
5	20 Gy + whole 30 Gy	0.28 (2.63)	2.41 (4.12)	1.89 (3.36)	16 w	–	–	0 #
6	20 Gy	0.22 (2.55)	1.28 (2.76)	1.63 (4.06)	75 w	–	–	20

* The value at the diagnosis of radiation necrosis, () the value before SRS, – no performance, w weeks, # autopsy.

65.3–98.6%) and 71.4% (95%CI: 29.0–96.3%), respectively [18]. Therefore, Cho/Cr ratios less than 2.48 in the spectrum of the lesion were defined as PSORN. In addition lesions removed by operation were studied by histopathology.

Protocol of treatment of PSORN

When a diagnosis of PSORN was suspected on Gd-MRI, ^{201}TlCl-SPECT, and ^{1}H-MRS, the initial treatment was conservative with steroids and/or heparin and warfarin. However, all patients suffered a gradual progressive worsening of their neurological condition. In four patients of the six, the ring-like enhanced mass (PSORN) was excised. In one of the other two patients the lesion was localized in the brain stem, and the other patient was in poor general condition.

Evaluation of the effect of treatment

The outcome (quality of life) was defined using the Karnofsky scale [17] after 75 weeks follow-up after diagnosis of PSORN.

Results

Table 1 summarizes data for the total radiation Dose, Cho/Lip, and Cho/Cr in ^{1}H-MRS at the diagnosis of PSORN and before SRS, the L/N in ^{201}Tl-SPECT at the diagnosis of PSORN and before SRS. It shows also the period of conservative therapy, the time up to excision, the degree of removal, and outcome for each patient.

Diagnosis

Although the differentiation between a recurrence of the tumour and PSORN was difficult in Gd-MR images alone, PSORN was diagnosed by ^{1}H-MRS in all 6 patients and by ^{201}TlCl-SPECT in 4 of 6 patients. In all 6 cases, Cho/Cr was less than 2.48 (mean: 1.77,

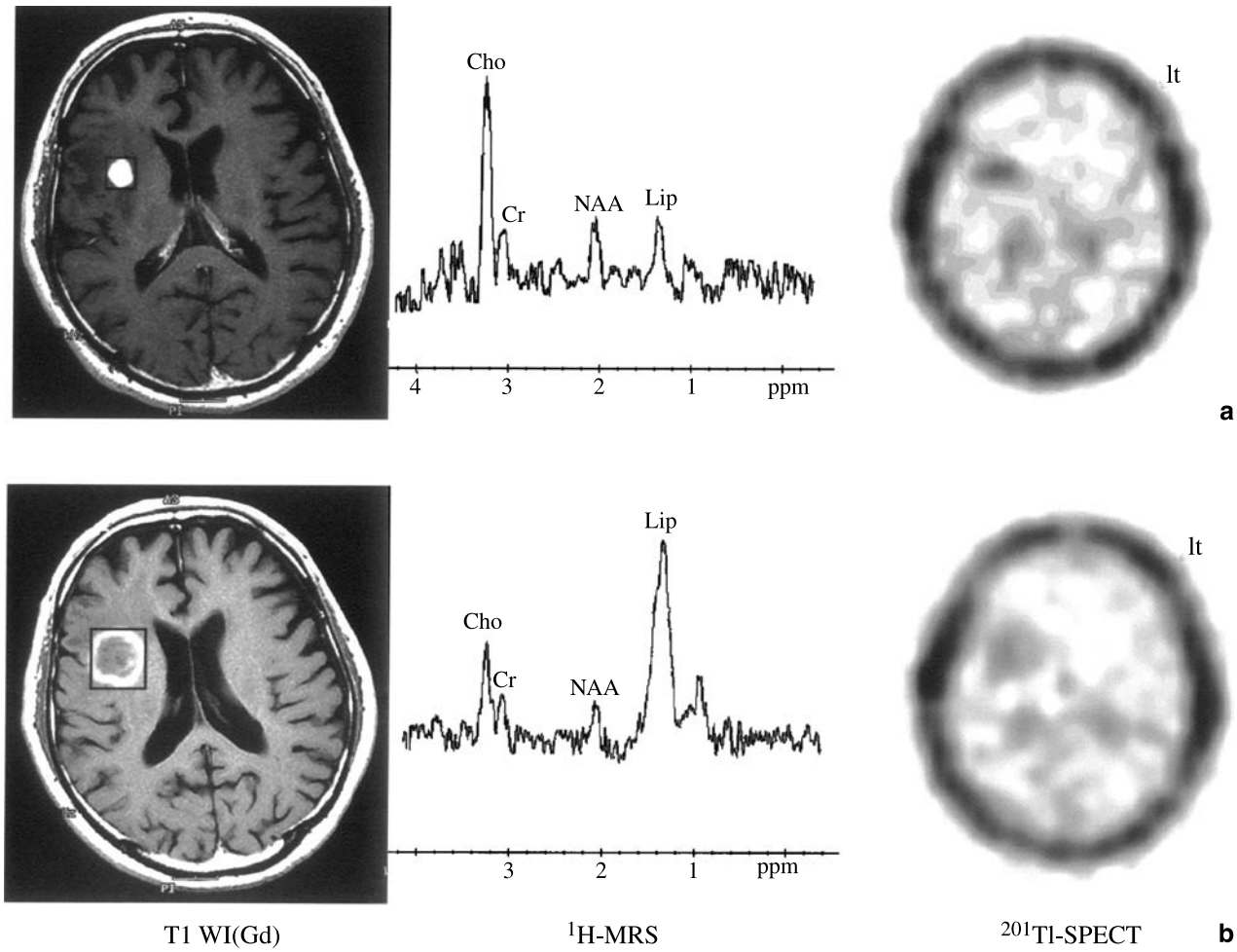

Fig. 1. Case 1. MRI shows an enhanced mass (ϕ 1 cm) with perifocal oedema in rt. basal ganglia, ^{1}H-MRS reveals high Cho signal Lip signal (Cho/Lip = 3.51, Cho/Cr = 3.14), and ^{201}TlCl-SPECT reveals high uptake (L/N = 2.84) in the lesion (a). MRI shows a ring-like enhanced mass (ϕ 3 cm) with perifocal oedema in rt. basal ganglia, ^{1}H-MRS shows high Lip signal (Cho/Lip = 0.26, Cho/Cr = 1.63), and ^{201}TlCl-SPECT shows high uptake (L/N = 1.95) in a lesion diagnosed as PSORN (b). MRI shows the enlargement of PSORN and perifocal oedema before excision of the lesion (c). MRI shows improvement of perifocal oedema after removal of the lesion (d).

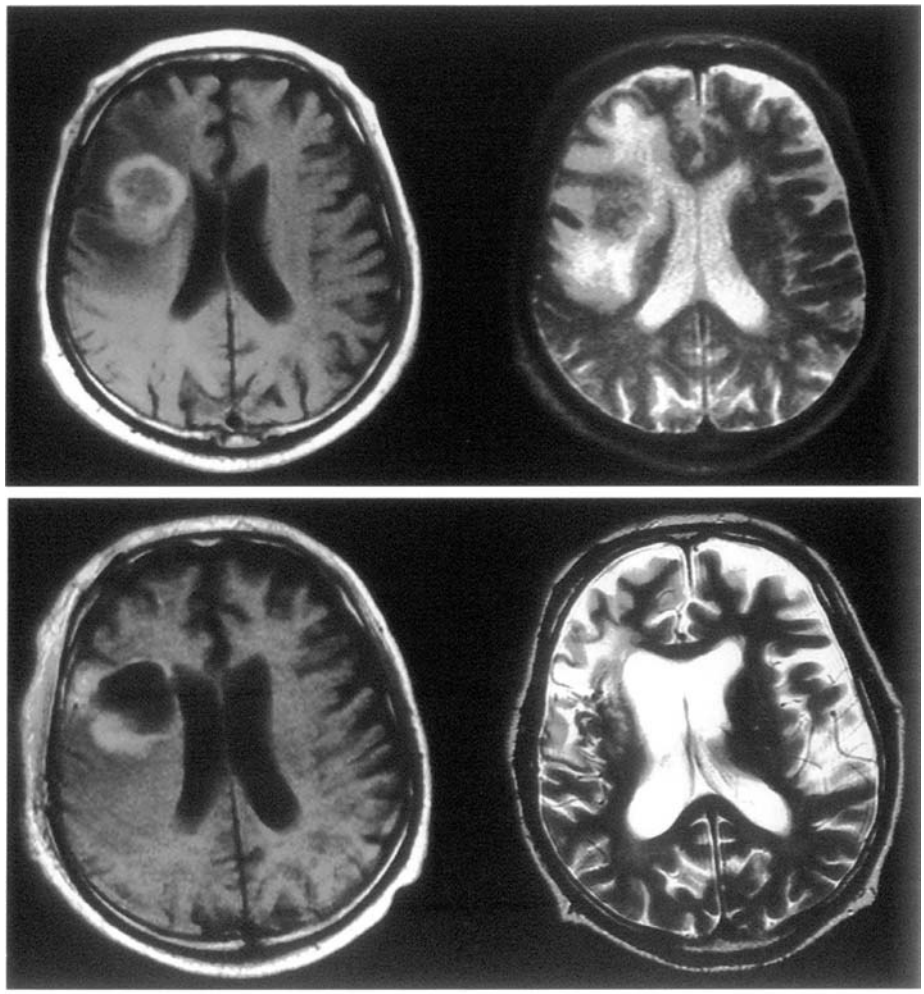

Fig. 1 (*continued*)

range: 1.21–2.41), Cho/Lip was less than 0.3 (mean: 0.23, range: 0.19–0.23) in ^{1}H-MRS. In ^{210}TlCl-SPECT, the mean L/N in radiation necrosis was 2.11 (range: 1.63–2.71).

Clinical course and treatments

In each patient, MRI showed PSORN as a ring-like enhanced mass with mass effect and extensive perifocal oedema. The perifocal oedema was related to the appearance of neurological deficit. In 4 patients, the lesion demonstrated by a Gd-enhanced rim and a non-enhanced inner region was removed. The neurological deficit and perifocal oedema improved. Quality of life improved in 2 patients who underwent excision of the PSORN lesion within 4 weeks from the time when conservative treatment became ineffective. However, in the other 2 patients in whom surgery was performed more than 16 weeks after the start of conservative treatment the deficit was progressive, and quality of life was not improved. The two patients who did not undergo surgery were treated conservatively but showed progressive neurological deterioration.

Histopathology

In 5 of the six patients, the diagnosis of radiation necrosis was confirmed by histopathological studies of the surgical specimen. In one of the 2 cases (case 6) treated conservatively, the diagnoses of radiation necrosis was based on ^{1}H-MRS and ^{201}TlCl-SPECT.

Illustrative cases

A patient who benefited from the excision of the lesion is presented below.

Case 1

A 60-year-old man had a symptomatic mass lesion in the right basal gangila shown by follow up MRI. He had renal cancer and had undergone a left nephrectomy 4 years previously. Histopathology showed a clear cell carcinoma. Two years previously he had a metastatic brain tumour in the left parietal lobe removed totally. One year after the brain tumour resection, an asymptomatic enhanced mass (ϕ 1 cm) was observed in the right basal ganglia on Gd-MRI. The lesion was diagnosed as a metastatic brain tumour by Gd-MRI, ^{1}H-MRS

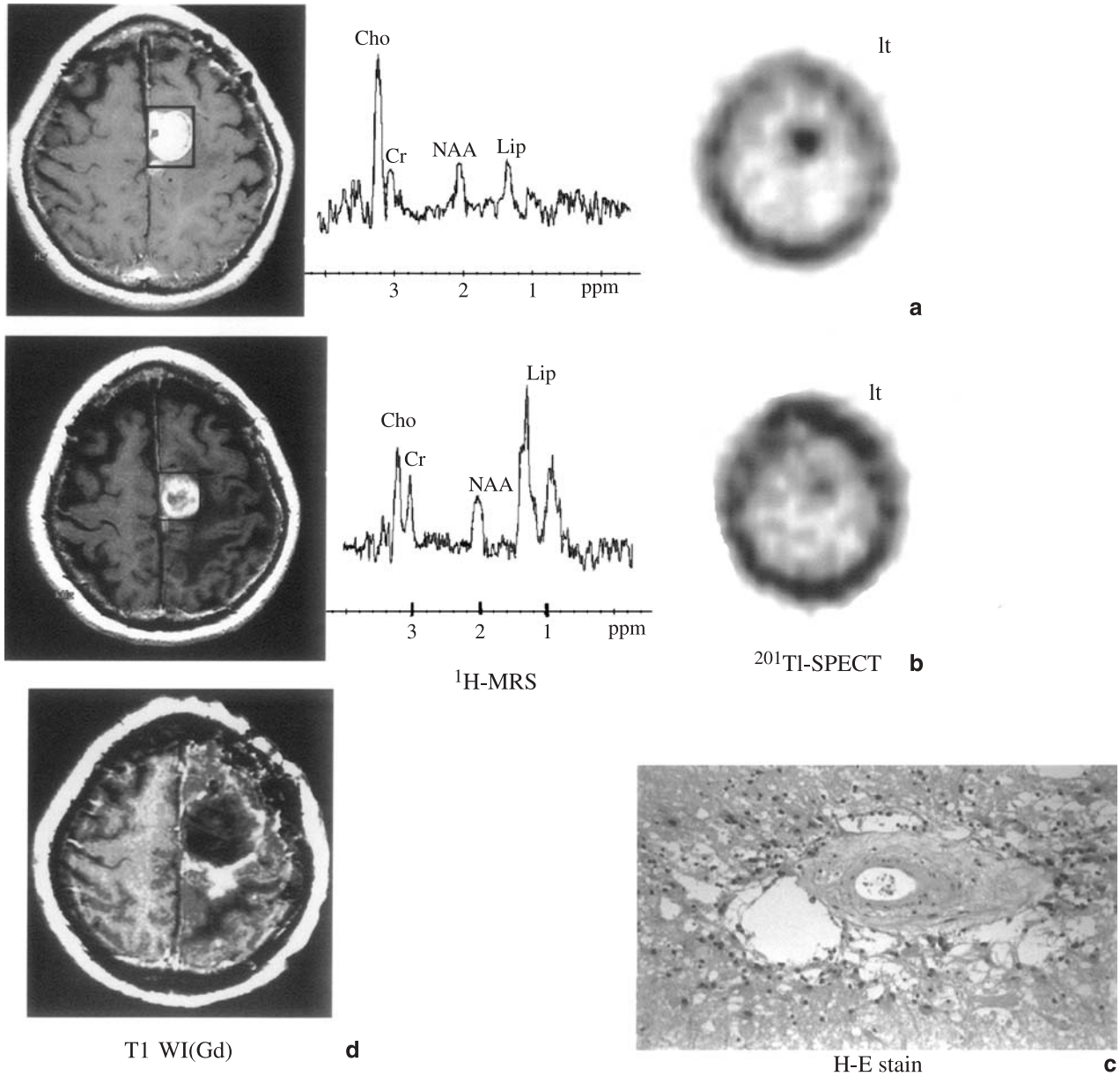

Fig. 2. Case 2. MRI shows an enhanced mass in the left frontal lobe, ^{1}H-MRS shows high Cho signal and Lip signal (Cho/Lip = 2.58, Cho/Cr = 2.94), and ^{201}TlCl-SPECT shows high uptake in the same region (L/N = 2.79) (a). Seven months after SRS, MRI shows a ring-like enhanced mass with perifocal oedema in the left frontal lobe, ^{1}H-MRS shows high Lip signal (Cho/Lip = 0.20, Cho/Cr = 1.21), and ^{201}TlCl-SPECT shows high uptake in the same region (L/N = 1.94) (b). Histopathological findings in tissue from the zone of Gd-enhancement on MRI (c). Postoperative MRI shows that there has been no reduction in perifocal oedema (d)

(choline-containing compounds (Cho)/mobile lipid (Lip) = 3.51, Cho/creatine and phosphocreatine (Cr) = 3.14), and ^{201}TlCl-SPECT (lesion (L)/normal (N) = 2.84) (Fig. 1a). SRS (cone size 10 mm, marginal dose 20 Gy, safety margin 1 mm) was performed. However, 8 months later he developed difficulty walking due to left hemiparesis, and a ring-like enhanced lesion with perifocal oedema was observed in the right basal gangila on MRI. It was diagnosed as PSORN by ^{1}H-MRS (Cho/Lip = 0.26, Cho/Cr = 1.63) and ^{201}TlCl-SPECT (L/N = 1.95) (Fig. 1b). His walking improved temporarily in response to conservative treatment with steroid, heparin and warfarin for 16 weeks, but thereafter he progressively deteriorated despite continuing the conservative therapy. MRI showed enlargement of PSORN and perifocal oedema (Fig. 1c). Total removal of the PSORN (lesion of the enhanced rim and inner non-enhanced region surrounded by rim on Gd-MRI) was performed at 4 weeks after the deterioration of the patient's ability to walk. The pathological diagnosis was radiation necrosis. After surgery, perifocal oedema on MRI (Fig. 1d) and gait disturbance were improved.

A patient who was not benefited by lesionectomy is presented below.

Case 2

A 68-year-old man had a 3-month history of difficulty in walking. Four years previously he had undergone a lobectomy of the right lung for what was shown histopathologically to be a well-differentiated adenocarcinoma. He had a metastatic brain tumour in the left frontal lobe removed 2 years later. One year before admission, an enhanced mass (ϕ 3 cm) was observed in the same region on Gd-MRI. The lesion was diagnosed as a recurrence of the tumour by Gd-MRI, ^{1}H-MRS (Cho/Lip = 2.58, Cho/Cr = 2.94), and ^{201}TlCl-SPECT (L/N = 2.79) (Fig. 2a). SRS (cone size 30 mm, marginal dose 20 Gy, safety margin 1 mm) was performed, after which the difficulty in walking disappeared for 7 months. However, difficulty walking due to weakness of the right lower limb appeared again, and gradually deteriorated. An enhanced mass with wide perifocal oedema was observed in the left frontal lobe on Gd-MRI, and was diagnosed as PSORN by ^{1}H-MRS (Cho/Lip = 0.20, Cho/Cr = 1.21) and ^{201}TlCl-SPECT (L/N = 1.94) (Fig. 2b), and conservative treatment with steroid, heparin and warfarin was begun. It was effective for 12 weeks, but then his gait disturbance gradually deteriorated and after sixteen weeks, total surgical removal of PSORN was performed. The pathological diagnosis was radiation necrosis (Fig. 2c). After surgery, perifocal oedema was slightly improved on MRI (Fig. 2d), but the symptoms and signs gradually progressed and he could not be discharged for rehabilitation.

Discussion

Surgical treatment of PSORN

There have been only a few reports [11, 15] of patients suspected to have a reccurent tumour in whom the perifocal oedema and clinical signs disappeared after removal of an area of radionecrosis. Although radio-induced necrosis is not a tumour in itself, the lesion progressively enlarges with mass effect and diffuse perifocal oedema in a way that resembles a neoplasm. This lesion is called progressive space-occupying radiation necrosis (PSORN) [30]. The mechanism responsible is subject to speculation. Damage of the endothelial cells by radiation leads to an increase in vascular permeability [6, 7], which produces perivascular oedema [22, 24] and demyelinization phenomena [2]. Vascular collapse in white matter may then interfere with the cerebral blood flow and energy supply to the tissue (in particular white matter) [5, 8], leading to brittle parenchyma, and prompting the appearance of an organization dissolution factor by the break down product of myelin and the response of microglial cells. This mechanism generates a vicious cycle and worsening pathological change [4]. The aim of surgical resection is to break the vicious cycle in PSORN.

Four patients underwent removal of a ring-like enhanced lesion (PSORN) on Gd-MRI. In two of these, removal was performed within 4 weeks after the time that conservative management became ineffective and the clinical sign and perifocal oedema on MRI were improved, as was quality of life. In contrast, in the other two patients who did not undergo excision within 16 weeks, the symptoms were gradually progressive. This indicates that removal of any PSORN should be performed at an early stage before the lesion becomes irreversible.

Diagnosis of PSORN

It is difficult to diagnose radio-induced necrosis using only CT and/or MRI, and it was recently reported that the findings of ^{201}TlCl-SPECT or PET enable differention between radio-induced necrosis and recurrence of a tumour [9, 23, 26]. Using ^{201}TlCl-SPECT, Endo *et al.*

reported that the positive predictive value of L/N ratios $\geqslant 2.5$ for diagnosis of recurrence of tumour was 83.3% and of L/N ratios <2.5 for diagnosis of radiation necrosis was 100% [10, 20]. Studies using ^{201}TlCl-SPECT enabled differentiation of radio-induced necrosis from recurrence of tumour in 4 of 6 patients.

Using a 1.5-tesla clinical MRI images to study ^{1}H-MRS, Chan *et al*. reported that the lactate peak was elevated in late delayed, radiation-induced injury [3]. On the other hand, Kamada *et al*. reported that radiation necrosis could be differentiated from recurrent glioma by use of the Lac/Cho ratio, which was <1 for recurrent glioma and >1 for radiation necrosis [16]. However, we did not observe a lactate-dominant signal and instead found a lipid-dominant signal in radio-induced necrosis. This does not contradict the report that a mobile lipid signal was detected in high grade glioma with necrotic tissue [19], but means that anaerobic metabolism was not possible in complete necrotic tissue. In another study, we found that the rate of misdiagnosis was lowest at a threshold level of 0.30 in the Cho/(Lip or Lac) and at a threshold level of 2.48 in the Cho/Cr ratio of the lesion [18]. The positive predictive values of a Cho/(Lip or Lac) ratio greater than 0.3 for diagnosis of metastasis and of a Cho/(Lip or Lac) ratio less than 0.3 for diagnosis of radiation necrosis were 94.4% (95%CI (confidence interval); 72.7–99.9.0%) and 100% (95%CI; 59.0–100%), respectively [18]. The positive predictive values of a Cho/Cr ratio greater than 2.48 for diagnosis of metastasis and of a Cho/Cr ratio less than 2.48 for diagnosing radiation necrosis were 88.9% (95%CI; 65.3–98.6%) and 71.4% (95%CI; 29.0–96.3%), respectively [18]. We therefore regarded threshold levels of 0.3 of the Cho/Lip ratio and of 2.48 Cho/Cr ratio of the lesion as differentiating radiation necrosis from tumour recurrence in each of six patients.

Prevention of PSORN

The total dose of radiation was over the safety margin in three of the six patients (2, 4, 5). This may be because the differential diagnosis between radio-induced necrosis and the recurrence of tumour could not be performed correctly before additional irradiation. In patients who received an overdose of irradiation, it was thought that the normal white matter might also be severely damaged, so that the lesion might be resistant to conservative treatment, and that the perifocal oedema might persist after removal of the lesion. It is important in the prevention of radio-induced necrosis that the initial SRS is accurately performed, and that excessive additional irradiation is avoided.

Conservative treatment for PSORN

Long-term medication with steroids is commonly used in the conservative management of radio-induced necrosis [21]. Histopathologically the enhancing rim around the low signal lesion on Gd-MRI consists of an inflammatory lesion with proliferation of capillaries and infiltration by inflammatory cells (Fig. 2c). Therefore, it is reasonable that steroids are remarkably effective. Fujii *et al*. proposed that steroids should be given immediately in this reversible stage of brain injury before irreversible ''necrosis'' occurs, and that steroids should be continued for periods of more than 12 months [12]. Anti-coagulant treatment with heparin and warfarin has also been reported to be effective in five of eight patients with radio-induced necrosis [14]. However, in our patients control of symptoms and signs either became dependent on steroids, or deterioration occurred despite administration of steroids.

Conclusion: Management of PSORN

Choosing between conservative treatment and excision can be difficult. Our experience indicates that, at present, the initial approach should be conservative, but if the symptoms and signs still advance or recur, it is better to excise the lesion at an early stage, before it becomes irreversible. Nevertheless we have studied only a small number of patients and more data are needed.

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Comment

Radiation necrosis is a major concern after sterotactic radiotherapy for brain tumours. The authors demonstrated well the results of differential diagnosis for radiation necrosis from the regrowth of the tumour by proton magnetic resonance spectroscopy (II-MRS) and single photon emission computed tomography (SPECT) with thallium-201 chloride (^{201}TlCl-SPECT). They clarified also the indication and favourable effect of lesionectomy for progressive space-occupying radiation necrosis.

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