Case report: Radiation-induced vasculopathy implicated by depressed blood flow and metabolism in a pineal glioma

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Abstract

A case of radiation-induced vasculopathy of a pineal glioma was presented with haemodynamic and metabolic changes before and after radiotherapy. After radiation of 60 Gy with conventional fractionation (1.8–2.0 Gy daily, 5 days per week), regional blood flow, oxygen extraction fraction, metabolic rate of oxygen, kinetic metabolic rate of glucose and the rate constants (K2, K3) were markedly depressed (20% or greater) compared with the pre-irradiated study. 7 months after radiotherapy, the patient developed transient episodes of both right and left upper limb convulsion, terminating in generalized convulsion. When she developed status epilepticus, computed tomography showed extensive low density areas in the territory supplied by the right middle cerebral and the right posterior cerebral arteries. Cerebral angiography revealed diffuse stenosis at both carotid bifurcations and at the origins of the right posterior communicating and posterior cerebral arteries. Haemodynamic and metabolic depression therefore implicated radiation-induced vasculopathy in the present case.

Adverse effects of radiotherapy on the brain are presented at acute and delayed stages. Radiation necrosis of the brain is an extreme example of irreversible brain damage at the late delayed stage. Neuroradiological investigations of computed tomography (CT) and magnetic resonance (MR) imaging often fail to predict the occurrence of brain damage induced by adverse effects of radiation. It is unclear whether the primary target for radiation injury in the brain is the capillary endothelial cell or the brain parenchymal cell. We have evaluated hemicirculatory and metabolic changes before and after radiotherapy in a series of patients with brain tumours. A wide variety of changes were found which varied from patient to patient at the early stage. An important factor was the influence of intracranial pressure. Oxygen and glucose metabolism tended to fall at the late stage (Mineura et al, 1988).

We report a case of radiation-induced vasculopathy, in which positron emission transaxial tomography (PET) monitoring of blood flow and metabolism indicates that there is a radiation hazard to the vascular system and brain parenchyma.

Case report

A 10-year-old girl with a 2 week history of vomiting and headaches was admitted to our hospital. She was

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clear and alert. No neurological abnormalities were noted except for optic disc edema secondary to increased intracranial pressure. Laboratory tests of blood showed normal values including a titre of tumour markers such as carcinoembryonic acid, alphafetoprotein, human chorionic gonadotrophin and placental alkaline phosphate.

CT of the head showed a ring-enhancing mass, 2×2.5 cm in diameter, in the pineal region and symmetrical hydrocephalus of the third and lateral ventricles. Cerebral angiography showed neither tumour blush nor tumour vessels. Because of continual symptoms of raised intracranial pressure, the patient underwent a ventriculoperitoneal shunt.

23 days after the shunting operation, PET was performed with the HEADTOME III. Regional blood flow (rCBF), blood volume (rCBV), oxygen extraction fraction (rOEF) and metabolic rate of oxygen (rCMRO₂) were measured using the ¹⁵O-labelled gas steady-state inhalation method (Mineura et al, 1986).

The rate constants of tracer transport from blood to brain (K1), reverse transport from brain to blood (K2), phosphorylation (K3), and the kinetic metabolic rate of glucose (rCMRGl) were determined using fluorodeoxyglucose (FDG) dynamic scanning after an intravenous injection of 185 MBq ¹⁸F-FDG (Sasaki et al, 1986). Autoradiographic rCMRGl was also calculated using Phelps' equation with Reivich's constants (K1 = 0.095, K2 = 0.125, K3 = 0.069, K4 = 0.0058) of normal brain tissue (Reivich et al, 1985).



Figure 1. CT scans after a shunting operation showed a ring-enhancing tumour in the pineal region. Left, non-enhancing CT; right, enhancing CT.



Figure 2. 15 O-labelled PET at the level of the pineal region before (upper) and after (lower) radiotherapy. The pineal lesion had a lower blood flow and oxygen metabolism. The blood flow and oxygen metabolism of the grey matter, especially the frontal and the temporo-occipital, fell markedly after radiotherapy.



Figure 3. Kinetic rCMRGl images before (upper) and after (lower) radiotherapy. The images were taken 20, 40 and 60 min after an intravenous injection of 185 MBq FDG. After radiotherapy, kinetic rCMRGl decreased in the grey matter. There was an abrupt depression of glucose metabolism 60 min after the injection in the temporal grey matter.

CT on the same day as the PET study showed no change in the enhancing focus except for improvement of the hydrocephalus (Figure 1). Values of each parameter of the tumour lesion were lower than those of the grey matter (Figures 2, 3 upper level).

The patient was tentatively diagnosed as having a pineal glioma, germinoma, or non-germinomatous germ cell tumour. Preoperative radiotherapy was chosen for diagnostic therapy to radiosensitive germinoma or to reduce the tumour mass to facilitate resection. A dose of 46 Gy was administered to the whole brain and a boost of 14 Gy to the tumour lesion in 32 fractions (1.8-2.0 Gy daily given 5 days per week) over 7 weeks using an opposing field technique and a 10 MeV linear accelerator. The tumour responded poorly to the 60 Gy target dose.

The second PET was performed 1 month after termination of radiotherapy. In the tumour lesion, all indices still remained low. Values of the right temporal grey matter, irradiated at a maximum of 60 Gy, were abruptly depressed compared with values of the preirradiated study (Table I, Figures 2, 3 lower). Because this depression implied radiation-induced suppression of blood flow and metabolism, radical operation was postponed. CT at the time of the second PET showed no abnormalities of the brain.

3 weeks after the time of the second PET study, the patient began to present with projectile vomiting and double vision, neurologically related to Parinaud's signs. Follow-up CT scans showed an increase in the size of the tumour mass to 2.5×3 cm. The cystic tumour was easily and extensively resected through a left occipital transtentorial route. Part of the tumour adhered to the surrounding brain structure of the tegmentum. Surgical specimens were composed of degenerative tumour cells, abundant necroses, and tiny nests of viable tumour cells. The histological diagnosis was that of malignant astrocytoma.

Postoperatively the patient's progress was uneventful. The Parinaud's signs diminished, and other symptoms cleared.

7 months after radiotherapy, clonic convulsion of the right or left upper extremity had developed, and progressed in the next 2 months to status epilepticus.



Figure 4. CT 7 months after radiotherapy showed extensive low density areas corresponding to the territories of the right middle cerebral and the occipital arteries (left, non-enhancing CT; right, enhancing CT).

CT showed extensive low density areas in the territories of the right middle cerebral and occipital arteries (Figure 4). Angiography showed diffuse stenosis of main cerebral arteries including internal carotid and anterior and middle cerebral. Posterior communicating and posterior cerebral arteries were severely stenosed.

The contralateral main arteries between carotid siphon and the initial portion of the anterior cerebral vessel were also stenosed (Figure 5).

In spite of medical treatment her neurological symptoms and signs including hemiparesis deteriorated progressively. Multiple hypodense areas on CT were

| Function (unit) | Control | Before | After | Change (%) |
|--|---------|--------|-------|------------|
| rCBF (ml per 100 ml min ^{-1}) | 88.4 | 48.2 | 37.3 | -23 |
| rCBV (ml per 100 ml) | 5.01 | 4.92 | 4.57 | -7 |
| rOEF | 0.27 | 0.47 | 0.34 | -28 |
| $rCMRO_2$ (ml per 100 ml min ⁻¹) | 3.16 | 3.87 | 2.27 | -41 |
| Autoradiographic rCMRGI (mg per 100 ml min ⁻¹) | 6.75 | 5.59 | 7.6 | +38 |
| Kinetic rCMRGl (mg per 100 ml min ⁻¹) | 6.33 | 5.52 | 3.98 | -40 |
| K1 (min ⁻¹) | 0.073 | 0.064 | 0.058 | -9 |
| K2 (min^{-1}) | 0.066 | 0.071 | 0.052 | -27 |
| K3 (min^{-1}) | 0.041 | 0.044 | 0.021 | -52 |

Table I. Quantitative measurement of blood flow and metabolism in the right temporal grey matter before and after radiotherapy

Control represents values of a 15-year-old girl with a pineal cyst.

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(b)

Figure 5. Cerebral angiography showed diffuse stenosis of main cerebral arteries including the internal, anterior, middle and posterior cerebral arteries: (a) right; (b) left.

seen in the left temporal lobe in addition to the right hemisphere. 10 months after the termination of radiotherapy the patient died.

Discussion

Radiation-induced vasculopathy, as firstly described by Lee and Hodes in 1967, is a recognized complication of radiation therapy. Kyoi et al (1989) summarized clinical features of the 21 reported cases in the literature. The disease frequently occurred in younger patients. Symptoms and signs appeared 4 months to 24 years after radiation. Clinical manifestations of this entity are not pathognomic and resemble those of cerebrovascular obstructive diseases, *i.e.* cerebral infarction, transient ischaemic attack and moyamoya disease. The primary diseases were mostly gliomas, and then pituitaryhypothalamic tumours. Doses varied from 24 Gy to 104 Gy; most cases had received a dose of between 50 and 70 Gy.

Brain tolerance to radiation is related to the number of fractions and the overall treatment time in days as well as to total dose. Isoeffect formulas, in terms of nominal standard dose (NSD) and equivalent dose (ED), are functions of time, dose and fractionation, and have been proposed to determine the threshold doses of the brain tolerance to radiation (Liebel & Sheline, 1987). Beaney et al (1987) measured temporal lobe rCBF, rOEF and rCMRO₂ in adult patients with pituitary tumours treated by irradiation. They concluded that, with properly fractionated (less than 2 Gy) megavoltage radiotherapy of total dose between 35 and 56 Gy, there was no significant fall in rCBF or rCMRO₂.

There seems to be no way to predict the appearance of this disease. CT and MR imaging do not depict ischaemic disorders until the symptoms are manifested clinically. Typical CT findings show low density areas corresponding to the territory responsible for obstructing vessels. Angiography revealed stenosis and obstruction of vessels located in the field of radiation (Mori et al, 1978; Mitomo et al, 1986; Katoh et al, 1990). Angiographical signs of the moyamoya syndrome develop as collateral pathways mostly in young patients (Servo & Puranen, 1978; Rajakulasingam et al, 1979; Okuno et al, 1985; Katoh et al, 1990). In the reported cases, the diagnosis was established after symptoms were presented.

In the present case, a total dose of 60 Gy was given with conventional fractionation (in 32 fractions of 1.8-2.0 Gy over 7 weeks). Blood flow and metabolism were evaluated by PET before and after radiotherapy. Although CT could not detect involvement of the brain parenchyma, PET images showed extensive perturbation of blood flow and metabolism. The values of the right temporal grey matter showed marked depression in rCBF and kinetic rCMRGl compared with those of a 15-year-old girl used as a similarly aged control, who was finally diagnosed to have a pineal cyst. After radiotherapy, all parameters except for autoradiographic rCMRGl fell sharply by 7–52% of the preirradiated values. PET clearly detected the haemocirculatory and metabolic disturbance of the irradiated brain, although retrospectively considered.

We calculated kinetic rCMRGl as well as autoradiographic rCMRGl using rate constants of the normal brain (Reivich et al, 1985). The two rCMRGl revealed dissociation; the former accurately evaluated changes of metabolism in the present cases. Kinetic rCMRGl studies with the rate constants of the respective regions may assist analysis of glucose metabolism in the pathognomic and perturbed brain tissue.

We previously described PET studies on the late effect of radiation on cerebral blood flow and metabolism. Although rCBF and rCBV varied widely, metabolism was depressed 3 months after irradiation in seven patients with gliomas. In these seven cases, there are no examples of radiation necrosis, and three cases are still alive without tumour recurrence. In a 13-year-old patient, a follow-up PET study more than 4 years after radiation showed some recovery from depressed metabolism. In contrast, the present cases showed a 20% or greater reduction in rCBF, rCMRO₂, kinetic rCMRGI, and the K1 and K2 rate constants.

In conclusion, PET measurements in the present patient treated by radiation indicated markedly depressed blood flow and metabolism, suggestive of radiation injury. PET will detect subtle changes of cerebral dysfunction induced by radiation.

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References

- BEANEY, R P, GIBBS, J S R, BROOKS, D J ET AL, 1987. Absence of irradiation induced ischaemic temporal lobe damage in patients with pituitary tumors. J. Neurooncol., 5, 129–137.
- KATOH, M, KAMIYAMA, H, ABE, H ET AL, 1990. Complete occlusion of right middle cerebral artery by radiation therapy after removal of pituitary adenoma. Case report. *Neurol. Surg. (Tokyo), 18,* 855–859 (in Japanese).
- KYOI, K, KIRINO, Y, SAKAKI, T ET AL, 1989. Therapeutic irradiation for brain tumor and cerebrovasculopathy. *Neurol. Surg. (Tokyo), 17,* 163–170 (in Japanese).
- LEE, K R & HODES, P J, 1967. Intracranial ischemic lesions. Radiol. Clin. N. Am., 5, 363–393.
- LEIBEL, S A & SHELINE, G E, 1987. Radiation therapy for neoplasms of the brain. J. Neurosurg., 66, 1-22.
- MINEURA, K, SUDA, Y, YASUDA, T ET AL, 1988. Early and late stage positron emission tomography (PET) studies on the hemocirculation and metabolism of seemingly normal brain tissue in patients with gliomas following radiochemotherapy. Acta Neurochirurgica (Wien), 93, 110-115.
- MINEURA, K, YASUDA, T, KOWADA, M ET AL, 1986. Positron emission tomographic evaluation of histological malignancy in gliomas using oxygen-15 and fluorine-18fluorodeoxyglucose. *Neurol. Res.*, 8, 164–168.
- MITOMO, M, KAWAI, R, MIURA, T & KOZUKA, T, 1986. Radiation necrosis of the brain and radiation-induced cerebrovasculopathy. *Acta Radiol. Suppl.*, *369*, 227–230.

- MORI, K, TAKEUCHI, J, ISHIKAWA, M ET AL, 1978. Occlusive arteriopathy and brain tumor. J. Neurosurg., 49, 22–35.
- OKUNO, T, PRENSKY, A L & GADO, M, 1985. The moyamoya syndrome associated with irradiation of an optic glioma in children. Report of two cases and review of the literature. *Pediatr. Neurol.*, 1, 311–316.
- RAJAKULASINGAM, K., CERULLO, L J & RAIMONDI, A, 1979. Childhood moyamoya syndrome. Postirradiation pathogenesis. *Child's Brain*, 5, 467–475.

REIVICH, M, ALAVI, A, WOLF, A ET AL, 1985. Glucose

metabolic rate kinetic model parameter determination in humans. The lumped constants and rate constants for $[^{18}F]$ fluorodeoxyglucose and $[^{11}C]$ deoxyglucose. J. Cerebr. Blood Flow Metabol., 5, 179–192.

- SASAKI, H, KANNO, I, MURAKAMI, M ET AL, 1986. Tomographic mapping of kinetic rate constants in the fluorodeoxyglucose model using dynamic positron emission tomography. J. Cerebr. Blood Flow Metabol., 6, 447–454.
- SERVO, A & PURANEN, M, 1978. Moyamoya syndrome as a complication of radiation therapy. Case report. J. Neurosurg., 48, 1026–1029.