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Case study

High prevalence of small vessel disease long after cranial irradiation

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ABSTRACT

Accelerated atherosclerosis of intra- or extracranial large arteries is a major cause of radiation-induced strokes. Recent development of MRI techniques has enabled detection of another important vasculopathy: microinfarcts or microbleeds after cranial irradiation. The purpose of this study was to investigate the incidence and characteristics of small vessel disease after cranial irradiation. MR images and clinical records of 102 outpatients who had undergone cranial irradiation to brain tumors were retrospectively reviewed. Only those who had undergone T_1WI, T_2WI, FLAIR, and T_2*WI during follow-up were included. Small vessel disease including small subcortical infracts, microbleeds, and volume of white matter lesions were assessed on the latest MR images of each patient. Ischemic or hemorrhagic stroke during the follow-up period was also reviewed. Twelve patients (mean age at the latest MRI, 38.5 years; 8 men) were assessed. The total radiation dose was 52.3 ± 9.7 Gy in these patients, 9 of whom received whole brain irradiation. Small subcortical infarcts (mean 2.3) were detected in 8 patients, microbleeds (mean 19.4) were detected in 11, and white matter lesion volume was 38.3 ± 11.6 ml. During the follow-up period of 19.8 ± 9.7 years, 5 patients experienced stroke (4 lacunar, 1 hemorrhagic). These strokes occurred as long as a median 21.9 (range, 10.4–30.2) years after cranial irradiation. In conclusion, small vessel disease is not a rare complication after cranial irradiation, even in young patients. Patients after cranial irradiation should be followed up with MR imaging including a hemosiderin-sensitive sequence.

1. Introduction

Radiotherapy is an effective therapeutic procedure for neck and brain tumors and contributes to improvement of patients' long-term survival [1]. However, cranial irradiation might cause late complications, including radionecrosis, cognitive impairment, cavernous malformations, or vasculopathy [2–7]. In addition, severe intracranial artery damage, including vascular changes, intimal hyperplasia and thrombosis, vessel stenosis, and occlusion might occur, which eventually results in subsequent stroke [8,9]. In previous reports, the incidence of neurovascular events in the population after cranial irradiation was 100-fold higher than in the general pediatric population [10]. Plummer et al. indicated that head and neck radiotherapy significantly increased the risk of transient ischemic attack and ischemic stroke [8].

Many cases of large intra- and extra-arterial stenosis that had caused subsequent stroke as late complications of radiotherapy were described in previous reports and studies [8,10–16]. In these, most authors suggested that atherosclerosis in large arteries accelerated by irradiation had caused atherothrombotic stroke [8,14].

Recently, small vessel disease such as lacunar stroke or microbleeds after cranial irradiation has attracted attention as an important radiation-induced cerebrovascular disease [17–20,29]. Shobha et al. reported the case of a patient with small vessel infarcts and microbleeds long after cranial irradiation [17]. In some studies, an advanced medical diagnostic MR imaging system detected an early phase of small vessel disease including microbleeds during long-term follow-up after cranial irradiation [18–20,29]. However, few studies have focused on the frequency, background characteristics, or prognosis of radiation-induced small vessel disease.

In this study, the aim was to evaluate the frequency and characteristics of small vessel disease after cranial irradiation to brain tumors and to determine the incidence of stroke related to cranial irradiation.

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2. Methods

2.1. Patients

MR images and clinical records of 102 patients who had undergone cranial irradiation to brain tumors between 1980 and 2000 at Kumamoto University Hospital were retrospectively reviewed. Excluded were those who had not undergone T_2*WI. Small vessel disease including small subcortical infracts, microbleeds, and volume of white matter lesions were assessed on the latest MR images of each patient. As part of usual follow-up, patients' MR images and neurological symptoms were checked each year.

Using patients' medical records, the following data were collected: age, sex, date of diagnosis, tumor type, tumor location, date of initial radiotherapy, radiation dose and fields (focal, extra focal, or whole brain), chemotherapy administration, hypertension, date of the latest MR imaging (follow-up period after initial cranial irradiation), and ischemic or hemorrhagic stroke during the follow-up period.

Subsequent strokes were confirmed by stroke symptoms and CT or MR imaging. In these patients, the following data were collected: age and date of stroke onset, time period between stroke onset and initial intracranial irradiation, location of stoke, and stroke subtype (TOAST) [21].

2.2. MR imaging

MRI was performed on one of three 3.0-T imaging systems (Siemens, General Electric, or Philips Medical Systems). Axial T_1-weighted images, T_2-weighted images, fluid attenuated inversion recovery (FLAIR) images, and T_2*-weighted images were obtained. The parameters in each sequence were as follows: T_1-weighted image (repetition time (TR) = 277–627 ms; echo time (TE) = 4.76–17 ms; flip angle (FA) = 70–90°; slice thickness 5–6 mm; 19–24 slices; matrix = 256–352 × 144–256); FLAIR image (TR = 8000–10000 ms; TE = 79–124 ms; FA = 90–180°; slice thickness 5–6 mm; 20–24 slices; matrix = 256–512 × 166–224); T_2-weighted image (TR = 3600–4430 ms; TE = 72–103 ms; FA = 90–180°; slice thickness 5–6 mm; 19–24 slices; matrix = 256–512 × 166–354); and T_2*-weighted image (TR = 500–900 ms; TE = 15–46 ms; FA = 18–35°; slice thickness 5–6 mm; 19–24 slices; matrix = 256–320 × 146–256). All brain images were reviewed by two neurologists who were blinded to clinical data.

2.3. Assessment of small vessel disease

Microbleeds were identified as small hypointense, circular or ellipsoidal signals that were less than 10 mm in maximum diameter on gradient-echo T_2*-weighted images. Vessels on consecutive slices, tumor, and cavernous hemangiomas were carefully excluded.

White matter volume on FLAIR images was measured using Quantomo software® (Cybertrial Medical Software Inc., Canada, 2011) [22]. White matter lesions that were likely caused by surgery were excluded.

Small subcortical infarcts were defined as parenchymal defects ≤15 mm in diameter in the regions of perforating arteries; they were hyperintense on FLAIR or T_2-weighted image or hypointense lesions on T_1-weighted images. Perivascular spaces and cortical infracts were not included.

2.4. Statistical analysis

To compare the background characteristics of patients who developed stroke and those who did not, Fisher's exact test was

Table 1
Background characteristics, findings of radiation-induced small vessel disease, and Patient events.

Case No.	Sex	Age at latest MRI, y	Age at radiation, y	Time from irradiation, y	Irradiation type	Total radiation dose, Gy	chemotherapy	HT	MBs	SSI	WML volume, ml	Event/ stroke type	Location of stroke	Stroke onset from radiation, y (age)	MRA
1	M	18	13	4.4	whole + focal	50	+	–	1	0	–	–	–	–	NP
2	F	23	12	10.5	whole + focal	50	+	–	3	0	–	–	–	–	NA
3	F	36	18	9.9	extended focal + focal	50	+	–	3	1	118.7	–	–	–	NA
4	M	64	48	8.5	whole + focal	78	+	–	0	0	59.8	–	–	–	NP
5	M	44	17	26.9	whole + focal	50	–	–	27	4	28.3	Lacunar	Rt. thalamus	26.8 (44)	NA
6	M	48	11	36	unknown	46	–	–	3	0	–	–	–	–	NA
7	F	38	17	21.1	extended focal + focal	50	+	+	5	3	27.8	Lacunar	Lt. corona radiata	10.4 (28)	NA
												Lacunar	midbrain	20.6 (38)	
8	M	37	11	25.1	whole + focal	55	–	+	55	9	13.9	Lacunar	Lt. corona radiata	22.3 (33)	NA
9	M	37	11	25.4	whole + focal	50	–	–	43	2	–	–	–	–	NA
10	M	49	16	29.5	whole + focal	45	+	+	41	7	18.2	Lacunar	Lt. thalamus	28.9 (45)	NA
												hemorrhage	Lt. putamen	30.2 (46)	
11	F	35	14	23.6	whole + focal	50	+	–	9	1	10.1	Lacunar	Lt. thalamus	14.1 (23)	NA
12	M	33	16	17.1	whole + focal	54	+	–	47	1	43.3	–	–	–	Lt. ICA top and MCA moderate stenosis

HT, hypertension: MBs, microbleeds: SSI, small subcortical infracts: WML, white matter lesions.
NA, no abnormality: NP, not performed: ICA, internal carotid artery: MCA, middle cerebral artery.

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