

CASE REPORT

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Radiation-induced glioblastoma occurring 35 years after radiation therapy for medulloblastoma: case report

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Abstract A 41-year-old man was admitted in June 2007 with a 1-month history of headache and cerebellar ataxia. At the age of 5 years, in May 1971, he had presented with headache, vomiting, and gait disturbance. Cerebral angiographical study demonstrated vascular shift caused by a mass lesion in the cerebellar vermis. He had immediately undergone partial removal. Histological diagnosis was medulloblastoma (MB). Postoperatively he received a total of 40 Gy radiation to the whole brain and 30.5 Gy to the spine without chemotherapy. He was again seen 35 years later with a radiation-induced glioblastoma (GB) that arose in the region of the original MB. The tumor was surgically removed, and he received radiotherapy and chemotherapy with ACNU, procarbazine, and vincristine. Postoperative irradiation reduced the size of the second tumor.

Key words Radiation-induced glioma · Medulloblastoma · OLIG2

Introduction

Malignant gliomas have been reported to arise in the radiation field of patients with previously radiation-treated brain tumors.^{1–3} Although the incidence of radiation-induced brain tumors is low at approximately 1%,⁴ it is an important complication. Brain tumors that develop after radiotherapy (RT) tend to be high-grade gliomas with astrocytic differentiation or glioblastoma (GB). The induction of second brain tumors by radiation-treated medulloblastoma (MB) has been documented; these tumors are more frequently seen in the cerebellum of children. In adults, they represent less than 1% of all brain tumors.^{5,6} Most recurrent MB are local in adults⁵ and children⁷; 75% recur within the first 2

years after initial treatment and 29% are seen after 5 years.

Here we report a 41-year-old man with a cerebellar glioblastoma that developed at the cerebellar hemisphere treated 35 years earlier by radiotherapy. The site of the MB was the cerebellar vermis; however, radiotherapy was performed for the whole posterior fossa. The second tumor manifested different histological features; it was diagnosed as a GB and fulfilled the criteria of radiation-induced neoplasm. Radiation-induced MGMT hypermethylation and p53 mutations may play a role in the development of a subgroup of radiation-induced gliomas (RIG),³ suggesting that these molecular alterations are directly involved in the genesis of postirradiation GB.^{2,4,8} We cannot unequivocally state that the GB in our patient is attributable to genetic changes because the 35-year interval between the first and second tumors appears to be excessively long. Our search of the literature found no other RIG arising after such a prolonged period after initial radiation treatment for MB.

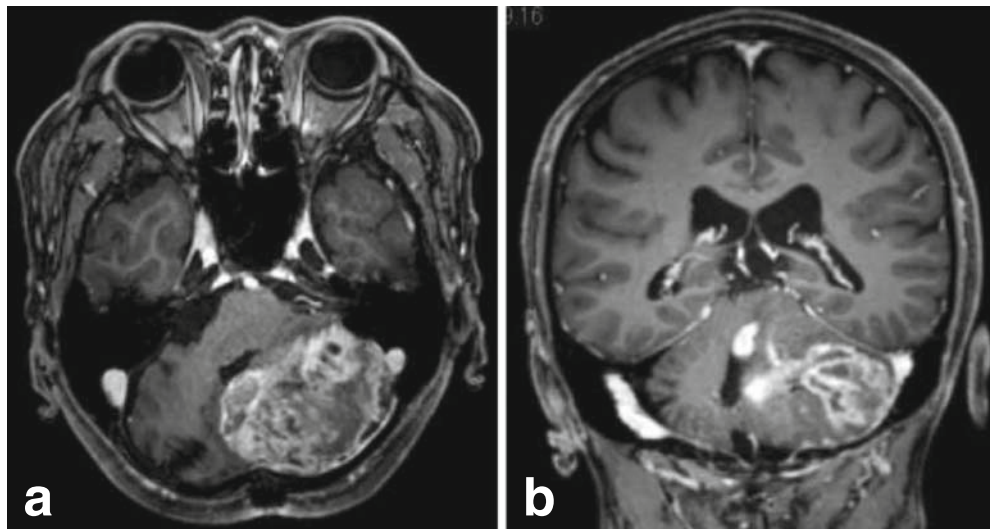
Case report

Clinical course

In May 1971, at the age of 5, this patient was first admitted to our hospital with headache, vomiting, gait disturbance, and neck stiffness. Neither he nor his family had any known genetic diseases predisposing to cancer. Cerebral angiography revealed a hypervascular mass lesion in the posterior fossa. The tumor, grossly totally resected in June 1971, was histologically diagnosed as an MB. Postoperatively, he received a total of 40 Gy radiation to the whole brain including the posterior fossa and 30.5 Gy to the spine without chemotherapy. During the next 15 years, he was regularly followed by computed tomography (CT) and magnetic resonance imaging (MRI) studies; there was no evidence of recurrence up to 1987, and thus follow-up was stopped. He was readmitted in June 2007 at the age of 41 years with a 1-month history of headache and cerebellar ataxia. CT

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Fig. 1. T₁-weighted gadolinium-enhanced magnetic resonance imaging (MRI) demonstrated a well-enhanced mass lesion in the left cerebellar hemisphere: **a**, axial; **b**, coronal



revealed a large, poorly delineated enhanced mass with areas of calcification at the original tumor site. MRI demonstrated an irregular well-enhanced mass lesion in the posterior fossa extending to the left cerebellopontine angle and suggesting brainstem invasion (Fig. 1a,b). The tumor was partially removed and diagnosed as a GB. His preoperative symptoms disappeared with the administration of ACNU, procarbazine, and vincristine and radiotherapy (50 Gy); although the size of the residual tumor decreased, he died of intratumor hemorrhage in January 2008 at the age of 42 years.

Pathological findings

Surgical specimens from the first (1971) and second operation (2007) were fixed, embedded in paraffin, and 4- μ m sections were prepared. The sections were deparaffinized in xylene and rehydrated in a graded ethanol-to-water series. Endogenous peroxidase activity was blocked with hydrogen peroxide. Histological study of the 1971 sample revealed a highly cellular neoplasm composed of cells with scanty cytoplasm and uniformly rounded nuclei and carrot-like cells; the morphological features were of classic MB (Fig. 2). Immunohistochemical staining was performed using the avidin–biotinylated enzyme complex (ABC) method (VECTASTAIN ABC kit; Vector Laboratories, Burlingame, CA, USA). Immunohistochemically, the neoplastic cells diffusely expressed the neuronal marker synaptophysin (data not shown). The tumor removed in 2007 manifested necrotic undifferentiated cells (Fig. 3a), prominent vascular proliferation (Fig. 3b), and pseudo-palisading (Fig. 3c). The mitotic rate was high; MIB-1 (DAKO) proliferation index was 61.7% (Fig. 3d). Immunohistochemically, the cells were slightly positive for glial fibrillary acidic protein (GFAP) (DAKO, Tokyo, Japan) (Fig. 4a), strongly positive for TUJ1 (Covance; The Development Services Company) (Fig. 4b), and negative for synaptophysin (DAKO). Their nuclei were strongly positive for OLIG2 (#18953 IBL; Gunma) (Fig. 4c,d). Based on these findings of necrosis,

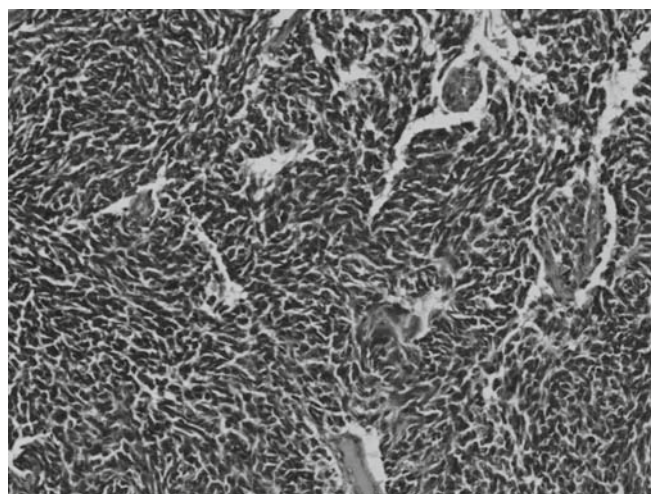


Fig. 2. Pathological findings on the tumor removed in 1971. Hematoxylin and eosin (H&E) staining demonstrated high tumor cellularity. The tumor contained cells with scanty cytoplasm and uniformly round nuclei

vascular proliferation, and pseudo-palisading, and the finding that MB cells are reportedly OLIG2 negative, we made a diagnosis of GB.

Discussion

RIG have been reported in patients who had previously been treated with radiotherapy (RT); the estimated cumulative risk for malignant brain tumors is 0.5%–2.7% at 15 years post-RT.³ Radiation-induced malignant glioma (RIMG) occurred within 10 years after RT in 81% of patients with acute lymphoblastic leukemia/lymphoma, in 59% of those with brain or other tumors, and in 18% with benign conditions.³ The RIMG was glioblastoma in 69 (75%) and anaplastic astrocytoma in 23 (25%) of 92 patients³ and was not correlated with sex, age at RT, the initial condition treated with RT, the RT dose or volume, surgery, or

Fig. 3. Pathological findings on the tumor removed in 2007. **a** H&E stain demonstrated necrosis (lower magnification). **b, c** H&E stain demonstrating the proliferation of endothelial cells (**b**) and pseudo-palisading (**c**). **d** MIB-1 staining showed a high mitotic rate and proliferative index (61.7%)

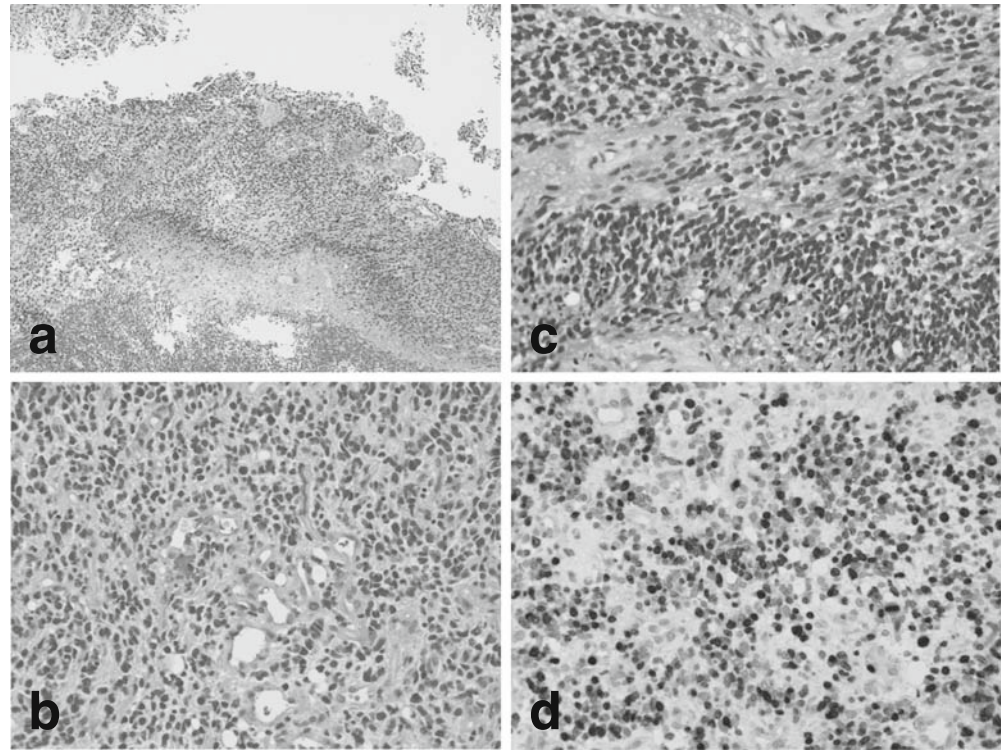
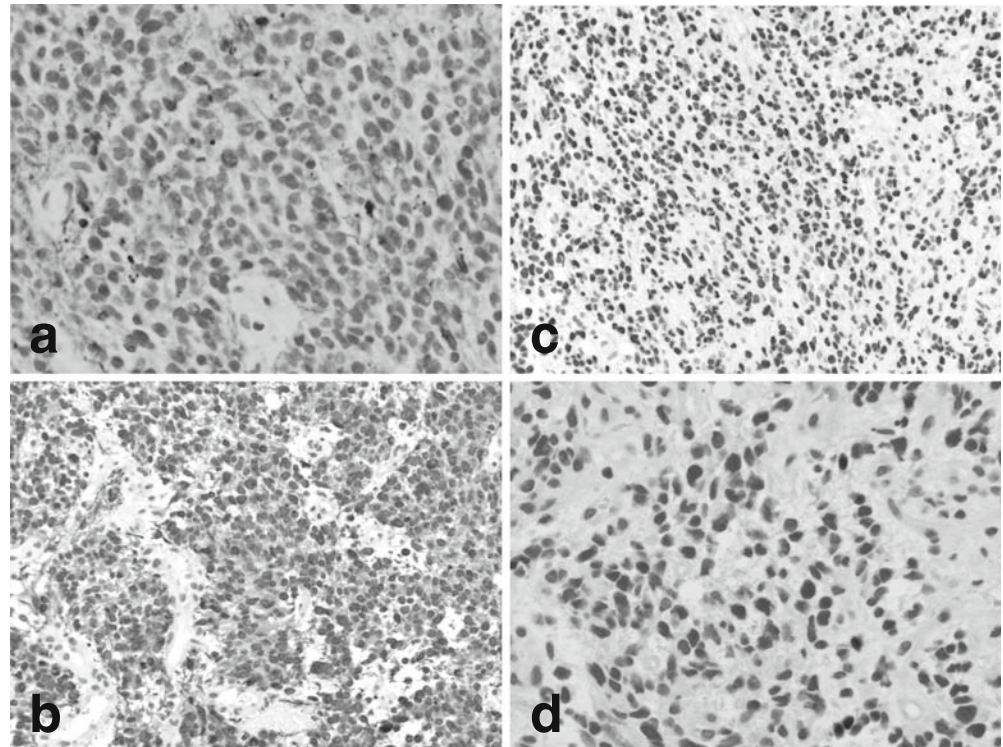


Fig. 4. Immunohistochemical staining of cells from the tumor removed in 2007. **a** Glial fibrillary acidic protein (GFAP) stain showed slight positivity. **b, d** The tumor cells were positive for TUJ1 (**b**) but negative for synaptophysin (**d**). **c** OLIG2 stain showed high nuclear positivity



chemotherapy. In our case the findings of hematoxylin and eosin staining were enough to diagnose a GB; however, the tumor cells did not represent pleomorphism and were somewhat small; therefore, strictly speaking, the diagnosis may be the small cell type of GB rather than GB multi-

forme. According to Salvati et al.,⁸ the mean latency for the development of radiation-induced brain tumors was 17 years (range, 6–26 years); they reported a correlation with both sex and age at the delivery of the first therapy. Our search of the literature found no patients whose RIMG was

Table 1. Reports of radiation-induced gliomas after treatment for medulloblastoma

Author (year)	Onset age (years), sex	Radiation dose (whole brain)	Radiation dose, posterior fossa	Radiation dose (spinal cord)	Latency to recurrence (years)	Histological diagnosis	Location
Kleriga (1978)	1, M	50 Gy	-	25 Gy	11	Malignant astrocytoma	Lt cerebellum
Pearl (1980)	5, M	30 Gy	10 Gy	20 Gy	13	Glioblastoma	Lt parietal lobe
Cohen (1981)	4, F	35 Gy	10 Gy	35 Gy	14	Malignant astrocytoma	Lt frontal lobe
Schmidbauer (1987)	13, M	60 Gy	-	-	6	Glioblastoma	Rt cerebellum
Safneck (1992)	2, M	44 Gy	10 Gy	36 Gy	9	Malignant astrocytoma	Lt optic nerve
Osumi (1994)	14, F	50 Gy	-	28 Gy	9	Malignant astrocytoma	Rt cerebellum
Furuta (1998)	8, M	40 Gy	15 Gy	30 Gy	15	Low-grade astrocytoma	Lt cerebellum
Nakamizo (2001)	11, M	30 Gy	24 Gy	30 Gy	9	Malignant astrocytoma	Rt cerebellum
Yang (2005)	18, F	30 Gy	20 Gy	30 Gy	9	Malignant astrocytoma	Fourth ventricle
Gessi (2008)	5, M	36 Gy	20 Gy	24 Gy	10	Glioblastoma	Lt cerebellum
Present case (2008)	7, M	20.8 Gy	59.8 Gy	30.5 Gy	8	Glioblastoma	Rt cerebellum
	7, M	20.8 Gy	-	-	35	Glioblastoma	Lt cerebellum

M, male; F, female; Lt, left; Rt, right

detected more than 30 years after initial RT (Table 1), although 9 of 129 (7.0%) arose in MB patients who had received adjuvant therapy.⁸

Preoperative MRI is helpful in reaching an exact diagnosis⁹ and in many cases MR spectroscopy (MRS) can demonstrate the tumor components. In our patient it was difficult to distinguish between radiation-induced GB and MB recurrence.

In a patient with RIG reported by Gessi et al.,¹ the genetic alterations were p53 mutation, loss of heterozygosity of 17p and 19q, O6-methylguanine-DNA methyl-transferase (MGMT) promoter methylation, and no amplification of epidermal growth factor receptor (EGFR). Although the immunohistochemical staining of p53 was negative in our case (data not shown), genetic alteration of p53 is always found in RIG. Gessi et al. stated that this pattern of genetic alteration is similar to that seen in secondary but not primary GB; however, the mechanism underlying the genetic alterations induced by radiotherapy remains unclear. Based on suggestions^{3,10,11} that patients reirradiated to address RIG exhibited longer survival times than those who did not receive RT, we delivered 50 Gy reirradiation in our case. Although reirradiation raises the risk of radiation necrosis, it resulted in a decrease in the size of the recurrent tumor.

Conclusion

We encountered a patient who presented with glioblastoma 35 years after undergoing partial removal and radiation therapy to treat medulloblastoma at the identical site in the brain as a child. This interval between the first operation and radiotherapy and the detection of a radiation-induced GB is longer than in previously reported patients.

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