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CASE REPORT

Radio-induced low-grade glioma: report of two cases and review of the literature

Alessandro D'Elia · Graziella Angelina Melone · Christian Brogna · Anna Formichella · Antonio Santoro · Maurizio Salvati

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Abstract With the increasing number of cancer survivors, we can observe a population that will present a higher risk of developing secondary long-term toxicities related to adjuvant chemo and radiotherapy regimens. Among these, children surviving from acute lymphoblastic leukemia (ALL) that were treated with prophylactic cranial irradiation represent a group of patients at a high risk of developing secondary brain tumors. Radiation-induced intracranial tumors have been documented since 1950, and today, more than one-hundred cases have been described. We report our experience with two young patients who were hospitalized for low grade gliomas and had a positive anamnesis for ALL and consequent radiotherapy.

Keywords Low-grade glioma · Radiation-induced glioma · Radiotherapy

Case reports

Case 1

A 32-year-old man was admitted to our institution for a 1-month history of simple partial seizure attacks, accompanied by aphasia and reading inability. He has been successfully treated 22 years earlier for acute lymphatic leukemia (ALL), with systemic chemotherapy (vincristine and prednisone), intrathecal methotrexate and cranial irradiation (18 Gy delivered in ten fractions during a period of 12 days). Neurological examination showed a slight sensorial dysphasia. A contrast-enhanced MRI study of the brain showed a left posterior temporal mass with a main diameter of 5 cm and no post-contrast enhancement (Fig. 1). A pre-operative functional MRI study (BOLD) with language task showed activation areas nearby and inside the lesion. An awake craniotomy was performed, and a language-stimulating brain mapping was done, achieving a safe total removal of the lesion (Fig. 2a, b).

A histological study demonstrated a grade II fibrillary GFAP+ astrocytoma according to WHO classification [1] (Fig. 2c): p53 protein was expressed and ki67 index was 1%. The postoperative course was uneventful and the patient completely recovered from his language disturbance. A spectroscopy MRI exam demonstrated the gross total removal of the lesion (Fig. 3a, b), with an aspecific Cho/NAA ratio compatible with a low grade glial lesion. No further treatment was planned, and the patient was doing well when last seen at follow-up control one year after neurosurgery. Further molecular analysis revealed the absence of loss of heterozigosity of chromosome 1p, 19q and 10q (i.e. LOH 1p 19q, and LOH 10q negative).

Case 2

This patient is a 34-year-old woman who underwent observation for a disorder of right hand fine movements. She was treated for ALL at age of 8, with a total brain irradiation of 24 Gy delivered in 12 fractions during a period of 19 days (no details on chemotherapy are

A. D'Elia (✉) · G. A. Melone · C. Brogna · A. Formichella · A. Santoro
Department of Neurological Sciences, Neurosurgery, Policlinico Umberto I, University of Rome "Sapienza", Rome, Italy
e-mail: deliaale@gmail.com

M. Salvati
Department of Neurosurgery, INM Neuromed IRCCS, Pozzilli (Is), Italy

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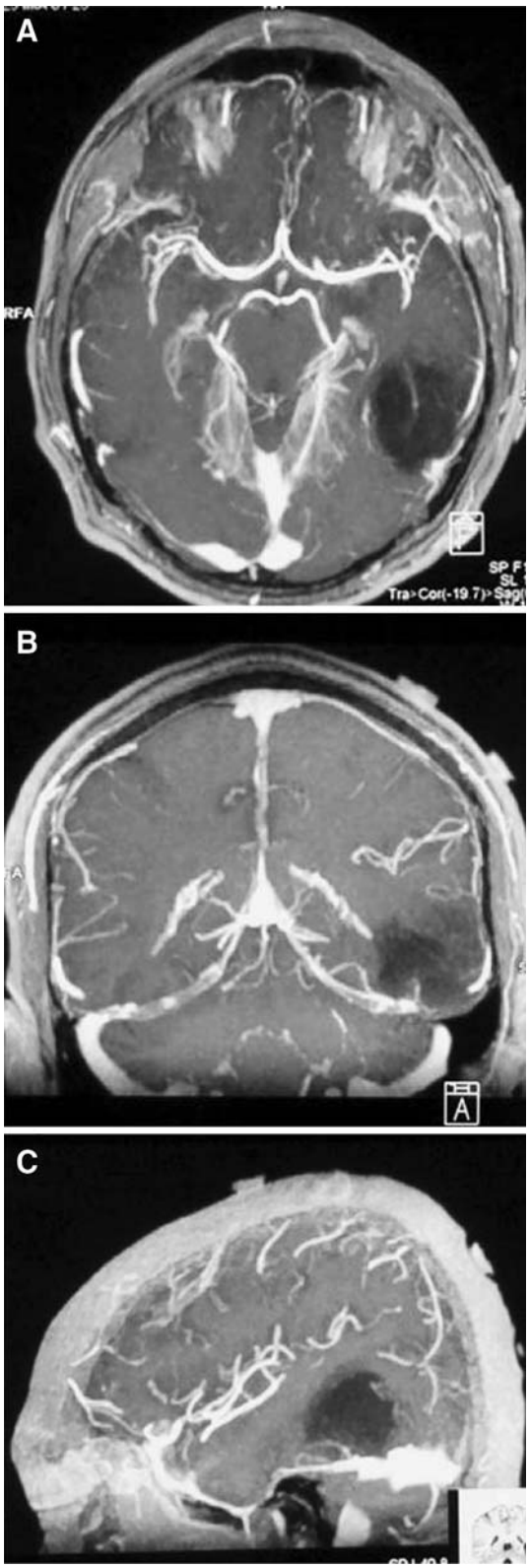

Fig. 1 Man of 32 years, preoperative imaging study: post-contrast MRI scan showing a left posterior temporal mass of 5 cm, with no enhancement, sited near sensory language cortex

available). Neurological examination showed a strength deficit of the right hand and a slight and transitory speech difficulty related to the motor component. Repeated EEG exams were not able to demonstrate any abnormality. Spectroscopy and functional (BOLD) MRI before and after gadolinium injection showed a 3-cm lesion situated under the left frontal supplementary motor area, with no inversion of Cho/NAA values, and with right-hand motor activation near the margins of the lesion (Fig. 4). An awake craniotomy was performed, with brain mapping for motor functions and registration of left mimic muscles and flexor muscles of the distal and proximal superior limb, and the resulting functional distribution of motor eloquent area enabled us to perform only a neuronavigation-guided biopsy. The lesion showed low cellularity and mild nuclear atypia (diagnosis: gemistocytic astrocytoma grade II WHO, Fig. 4d). Postoperative not fluent aphasia developed and completely recovered in 3 days, although a light strength deficit of the right hand still remained, that was comparable with the preoperative status. At 6 months from neurosurgery, neurologic status is unvaried.

Discussion

Although therapeutic X-irradiation is a suitable procedure for treating many intracranial pathologies, especially tumors, it represents the only environmental factor unequivocally associated with an increased risk of brain tumors [2]. To be termed 'radio-induced', the secondary tumor must present the following features, as defined by Cahan in 1948 [3]: (1) the tumor must originate in the previously irradiated region; (2) there must be a sufficiently long time interval from irradiation to the onset of postradiation tumor; (3) the histotype of the tumor must be different from the primary one; (4) the patient must not suffer from pathologies favoring the development of tumors, such as von Recklinghausen's disease, Li-Fraumeni's disease, tuberous sclerosis, xeroderma pigmentosum etc. The most common radiation-associated tumors are sarcomas and meningiomas, while malignant gliomas are rather rare [2, 4]. Even rarer are low grade radioinduced gliomas: by reviewing the literature in another paper [5], we found 129 published cases of primitive brain gliomas that could be related to previous irradiation for varies pathologies, but only 22 of these were low grade gliomas (Table 1).

Regarding the first disease, it appears that gliomas occur more frequently in patients treated as children for acute lymphoblastic leukemia (ALL) [6–8]: this fact may be related to the contemporary administration of intrathecal chemotherapeutic agents, or to the propensity of leukemia

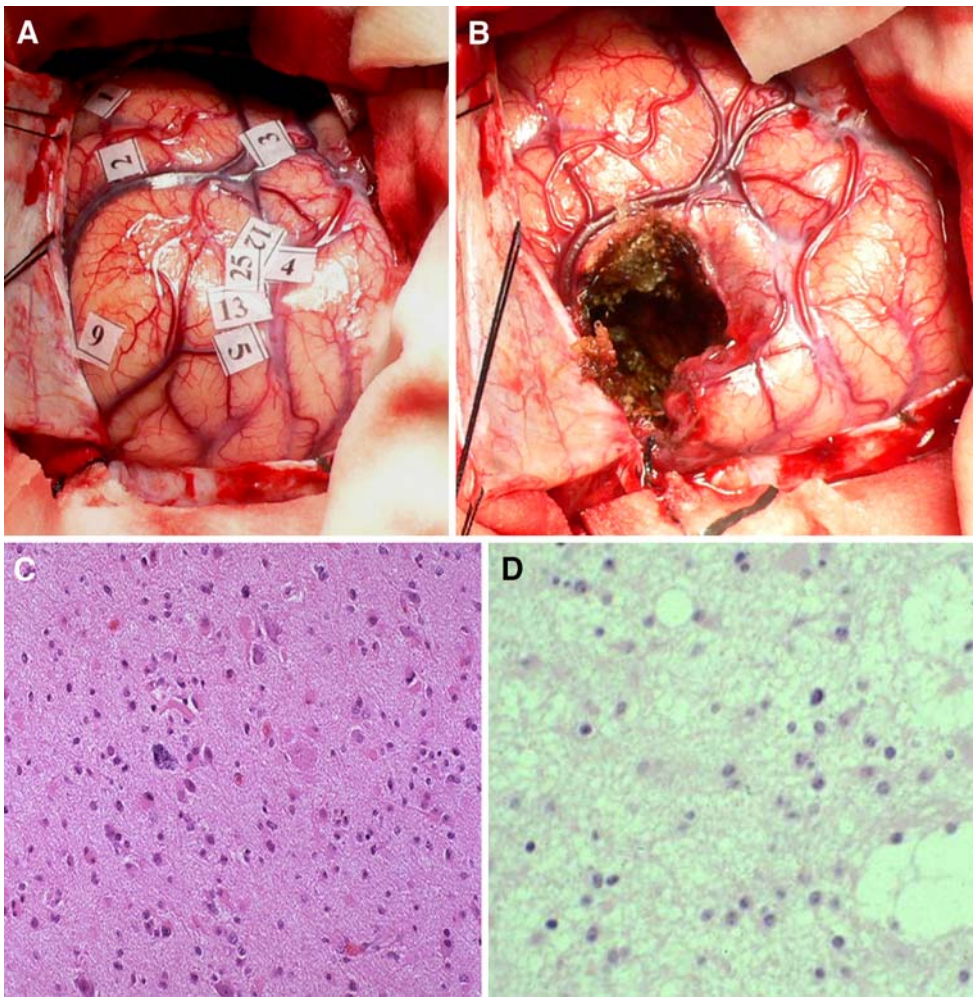

Fig. 2 Case 1: language brain mapping during surgery (**a**): the numbers identify critic areas causing speech arrest or errors when stimulated; stimulation was performed even on subcortical white matter pathways. At the end of stimulation, we obtained a safe surgical cavity (**b**). Hematoxylin–eosin stained specimens (×250 **c**, ×400 **d**) shows low cellularity and presence of mild nuclear atypia with rare gemistocytic elements (diagnosis: fibrillary astrocytoma grade II WHO)

itself to favor tumors of the glia [9, 10]. However, X-rays remain the most well-established mutagenic agent [11].

The two cases described were both treated as children for ALL. The average dosage of irradiation was of 24 Gy in one case and 18 Gy in the other, with single fractions of 2 and 1.8 Gy, respectively: these data are compatible with those found in previously published series [5, 8, 12, 13]. Regarding latency period, it has been reported that median latency for high-grade gliomas ranges from 9.1 to 11 years, whereas for meningiomas it reaches 19 years [8, 14, 15], although a longer latency was reported in other studies [5]. For low-grade radioinduced gliomas, range is from 1 year to 36 years (Table 1), and in our two cases latency was 26 and 22 years: these values are higher than those reported in the literature for high-grade gliomas, but we must consider that a low-grade glioma has an indolent course, and takes many years to develop and manifest clinically [16]. Hence, we do not know when our cases of grade II astrocytoma began their slow growth, and consequently neither do we know the true latency interval.

Diffuse astrocytomas are uncommon gliomas: they represent about 10% of all gliomas, with an incidence rate of 0.13 per 100,000 person per year in the United States [17]. The mean overall survival after resection is about 6–8 years, with great individual variability [1, 18]. The course of the disease is mainly dependent on the malignant transformation to glioblastoma multiforme, which usually occurs after 4–5 years. The most important prognostic factors for good outcome are young age and grossly total tumor resection [1, 18], factors both present in our cases. On the other hand, little is known about clinical outcome of radio-induced low-grade gliomas. It has been thought that radiation-induced malignancies may possess some clinical features slightly different from their 'idiopathic' counterpart [19, 20], but this fact regards high-grade gliomas occurring in younger age and atypical sites, and not referable to our two cases. In fact, age in our patients is typical for histotype [1], and sites involving eloquent areas are very common for low grade gliomas [18]. About molecular characterization, it was performed only in the

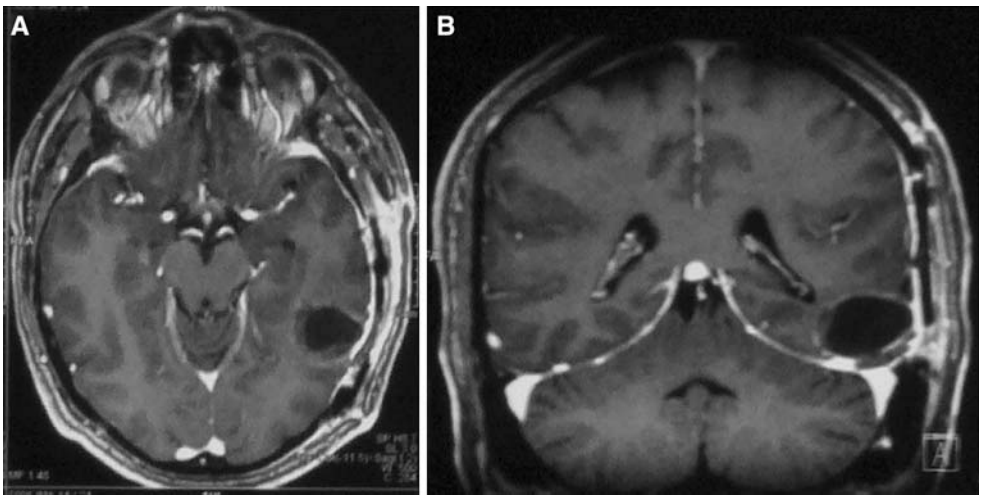

Fig. 3 Case 1: a contrast-enhanced postsurgical examination shows the gross total removal of the lesion (**a** assial, **b** coronal view)

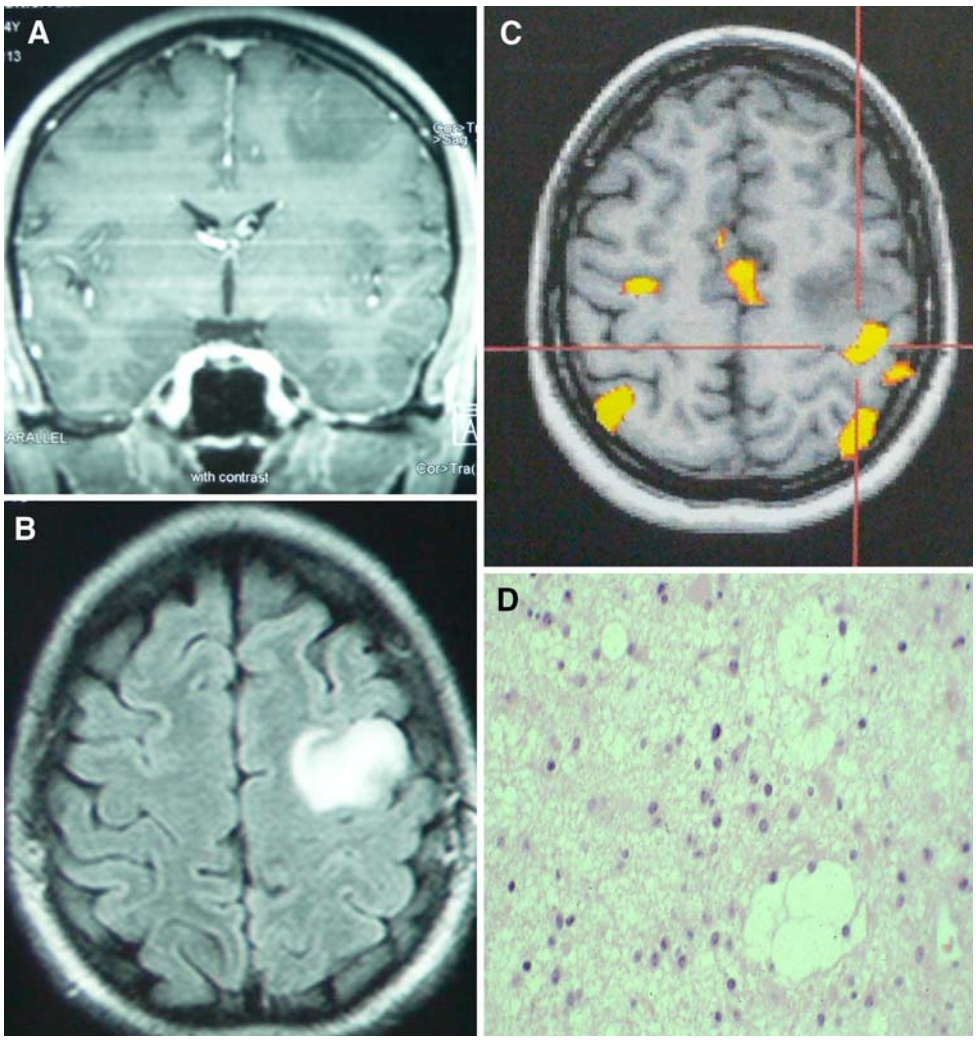

Fig. 4 Case 2: post-contrast coronal T1 sequence shows a not-enhancing hypointense 3 cm lesion sited under the left frontal supplementary motor area (**a**) that becomes hyperintense at assial inversion recovery (**b**). Functional blood-oxygen level dependent (BOLD) acquisition shows activation areas at precentral gyrus nearby the lesion when sentences are pronounced (motor speech activation). Histological specimen (hematoxylin–eosin stain, ×250) demonstrates the low cellularity and the diffusion of tumor cells (diagnosis: astrocytoma grade II WHO) (**d**)

first case described, because of the lack of sufficient tissue for molecular analysis of the second reported case. The absence of LOH 1p 19q, and 10q is typical of common diffuse astrocytomas of II grade of the general population [1]. It was observed that radiation-induced cranial tumors usually have a malignant histotype [5], but this fact can not

Table 1 Main features of radiation-induced low-grade gliomas described in literature, including our cases (adapted from [5])

	Author	Age/sex	1st disease	Dose (Gy)	Latency (years)	Radio-induced glioma
1	Jones	33/M	Meningioma	40	10	Astrocytoma
2	Albert	4/M	Tinea capitis	5–8	4	Astrocytoma
3	Albert	10/M	Tinea capitis	5–8	1	Astrocytoma
4–5	Shore	2 M	Tinea capitis	3–4	5–6	Astrocytoma
6	Shore	8/M	Tinea capitis	3–4	26	Cerebellar astrocytoma
7	Walters	3/F	ALL	26.2	6	Astrocytoma
8	Anderson	25/F	Medulloblastoma	42	6	Cerebellar ependymoma
9	Okamoto	25/F	Medulloblastoma	42	6	INFT ependymoma
10–14	Albo	3M–2F	ALL	24	6.5	4 Astrocytoma + 1 ependymoma
15	Malone	8/F	ALL	20	3.5	IFNT and spinal astrocytoma
16	Malone	19/M	ALL	25.2	4.5	Astrocytoma
17	Dierssen	16/F	Fibrosarcoma	50	11	Astrocytoma
18	Dierssen	15/M	Ear chronic disease	18	11	Astrocytoma
19–20	Soffer	2F	Tinea capitis	?	?–36	Cerebellar + Fibrillary astrocytoma
21	Tsang	38/M	Pituitary adenoma	50	9	Astrocytoma
22	Walter	2/M	ALL	24	9.2	Oligodendroglioma
23	Present report	32/M	ALL	18	22	Astrocytoma
24	Present report	34/F	ALL	24	26	Astrocytoma

be related to low-grade radiation-induced gliomas, even at a molecular level, as shown by our case, even though more data on molecular analysis are expected. About clinical outcome, only a longer follow-up will be able to provide more data: we are particularly interested in time to progression and growth rate of this particular subtype of low-grade gliomas, and we hope that observation of more cases in the future will shed some light on this topic.

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