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BRIEF COMMUNICATION

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# Radiation-induced tumors of the central nervous system occurring in childhood and adolescence

## Four unusual lesions in three patients and a review of the literature

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**Abstract** The authors report four very rare radiation-associated tumors (or radiation-induced tumors; RITs) of the central nervous system (CNS) and review the literature on this topic. The purpose of this study was to determine the possible relationship between the harmful effects of radiation therapy, the shortest and the longest interval between the time of irradiation and the occurrence of the secondary tumor, and possible predisposing factors. The tumorigenic effects of therapeutic irradiation of the CNS have been mentioned in the literature, but the authors' literature search did not disclose either many reports of cases such as their own or a satisfactory and concise discussion on the different aspects of the late and catastrophic complications of this method of adjunct therapy to the CNS. Four rare cases of RIT in three patients are presented: a unique case of intradural meningioma of the cervical spine, which was irradiated successfully only for the patient to present with a new high-grade cerebral astrocytoma 4 years later, a paraventricular cavernoma and a fronto-temporo-orbital chondrosarcoma. These second RITs became symptomatic in the 17th, 16th and 15th years of life, respectively, in these young patients. The primary lesions were ependymomas, two in the IV ventricle and one in the left hemisphere. The time intervals between radiation and secondary tumor presentation were 14 and 18 years, 9 years and 28 months, in the order in which these patients presented. All the patients survived the second operation except the one with chondrosarcoma, who died in spite of repeated surgical interventions and adjunct therapies. It is concluded that the development of secondary RITs does not necessarily require a very long time interval; that although sarcomas are the most common RITs of the CNS in childhood and adolescence, benign and other rare and curable lesions may also occur in the field or vicinity of the field of radiation; and that in view of the possibility of occurrence of different types of RITs after varying time intervals in a single patient, whole-life follow-up of similar patients is mandatory.

**Keywords** Cavernoma · Childhood · Chondrosarcoma · Meningioma · Radiation therapy

## Introduction

Radiation-induced or secondary tumors are well-documented sequelae of therapeutic irradiation. Even though they are infrequent, several types of tumors have been reported to develop after irradiation of the head and neck region: sarcomas, meningiomas and even vascular malformations [40]. Only 34 cases of radiation-induced sarcomas (RIS) of the CNS had been reported up to late 1995 [4–8, 10–12, 28, 35, 44]. These include meningio-

sarcomas, neurofibrosarcomas, pleomorphic cell sarcomas, fibrosarcomas, malignant fibrous histiocytomas, gliosarcomas [12, 22, 38, 39, 46, 47, 57], and a single report of chondrosarcoma [8]. Postirradiation meningiomas (PRM) have been defined as a well-known nosological subgroup among the RITs with distinct clinical and histological characteristics [7, 9, 22, 26, 33, 34, 36, 39, 42, 49, 50, 60]. Among the cases of radiation-induced meningiomas (RIMs) reported in the English literature, we encountered only two cases of spinal radiation-induced meningioma (RISM) [23, 41]. It is accepted as fact that some of the occult cerebral vascular malformations (OVM) and cavernomas are radiation-induced lesions [2, 13, 20, 29, 30, 44, 61] not visible on previous images recorded for the patients, as in our unique case of radiation-induced cavernoma (RIC).

We now report four RITs (or radiation-associated tumors) of the CNS occurring in three patients, all during childhood and adolescence. We will concentrate on; (a) the rarity of the reported cases, (b) the tumorigenic mechanisms of radiation therapy to the CNS, and (c) the possible effect of delivering radiation during childhood on the latency period, leading to development of a second tumor in the adolescence.

## Case reports

Case 1

This 17-year-old girl had been admitted to the Department of Neurosurgery, Hadassah University Hospital, at the age of 22 months with torticollis and irritability. The neurological examination at that time was negative except for mild papilledema, left-sided hypotonia and a broad-based gait. CT scanning revealed a large space-occupying lesion located within the left cerebellar hemisphere and impinging on the IV ventricle (Fig. 1A). She was operated on by Prof. A. Sahar, who encountered a very large left cerebellar hemispheric ependymoma; gross total resection was achieved. Her left-sided hypotonia improved with time. She received a full course of irradiation in Hadassah Radiation and Clinical Oncology Department, receiving 4500R to the whole brain and 2000R to the spine, while separation fields were calculated on C2 and the cervical spine was shielded at the time of brain irradiation. The patient grew normally and was fit to attend school afterwards. At the age of 17, she developed a slight gait problem and occasional nocturia. On physical examination, she was found to be spastic and paraparetic, with equal weakness in the upper and lower extremities, which was rather more pronounced on the right side. A fine pin-prick sensory level could be detected on the left half of the trunk up to the level of the C6/7 dermatome. Control CT scanning of the brain did not show any intracranial lesion, while magnetic resonance imaging (MRI) of the spine (Fig. 1B) revealed a cylindrical mass with wide dural base located to the right of the spinal cord, extending from C6/7 down to T1/2. The tumor was moderately hyperintense in the T1-weighted image and enhanced homogeneously after gadolinium injection. At operation, an intradural, right dorsolaterally located tumor mass measuring 4×2.5×2 cm was removed in pieces. Most of the dural attachment of the tumor was excised, and the dural edges were curretted and coagulated using bipolar cautery. Dura was repaired using autogenous fascial graft. The diagnosis noted in the histopathology re-

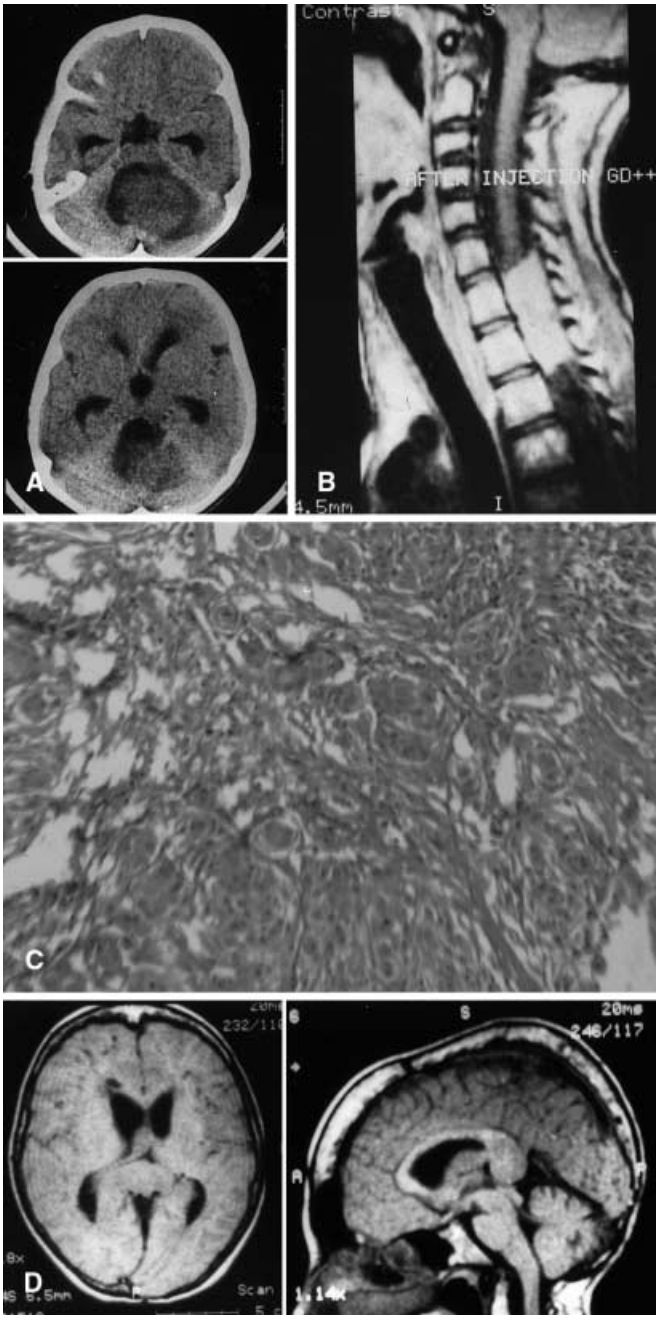



**Fig. 1 A** Contrast-enhanced CT scan revealing a nonhomogeneously enhanced tumor within the IV ventricle. Dilatation of the temporal horns and anterior III ventricle indicating the obstructive hydrocephalus. **B** Sagittal T1-weighted MRI (postcontrast) showing enhancement of an extramedullary tumor. **C** Histological features of a syncytial meningioma with tumor cells arranged in sheaths and loose whorls. The individual cells are polygonal with uniformly staining cytoplasm throughout the tumor. H&E, ×105. **D** Postcontrast MRI (in horizontal and sagittal planes) 4 years after resection of the cervical RI meningioma, showing the infiltrative glioma extending from within the III ventricle along the fornices to both hemispheres

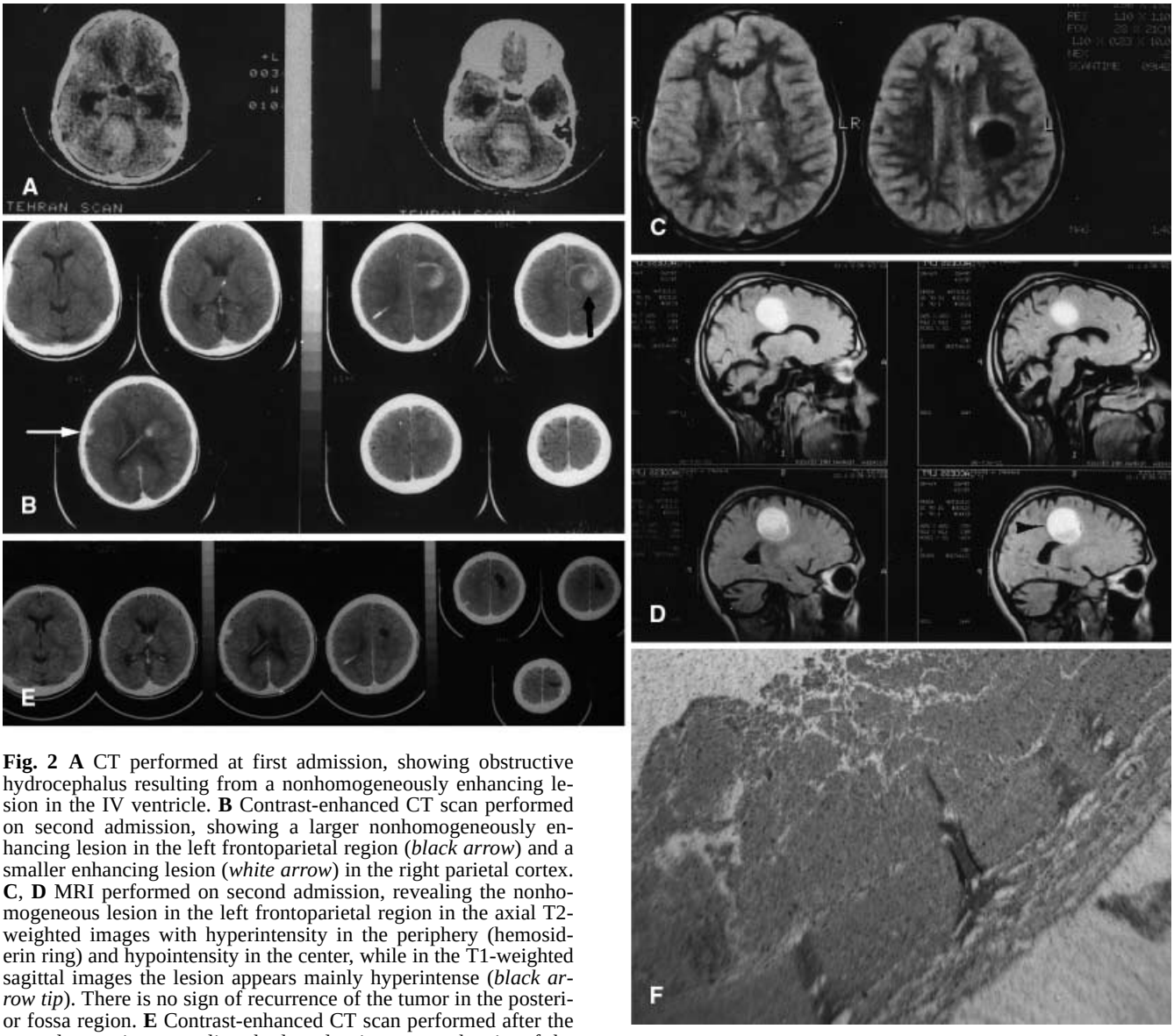
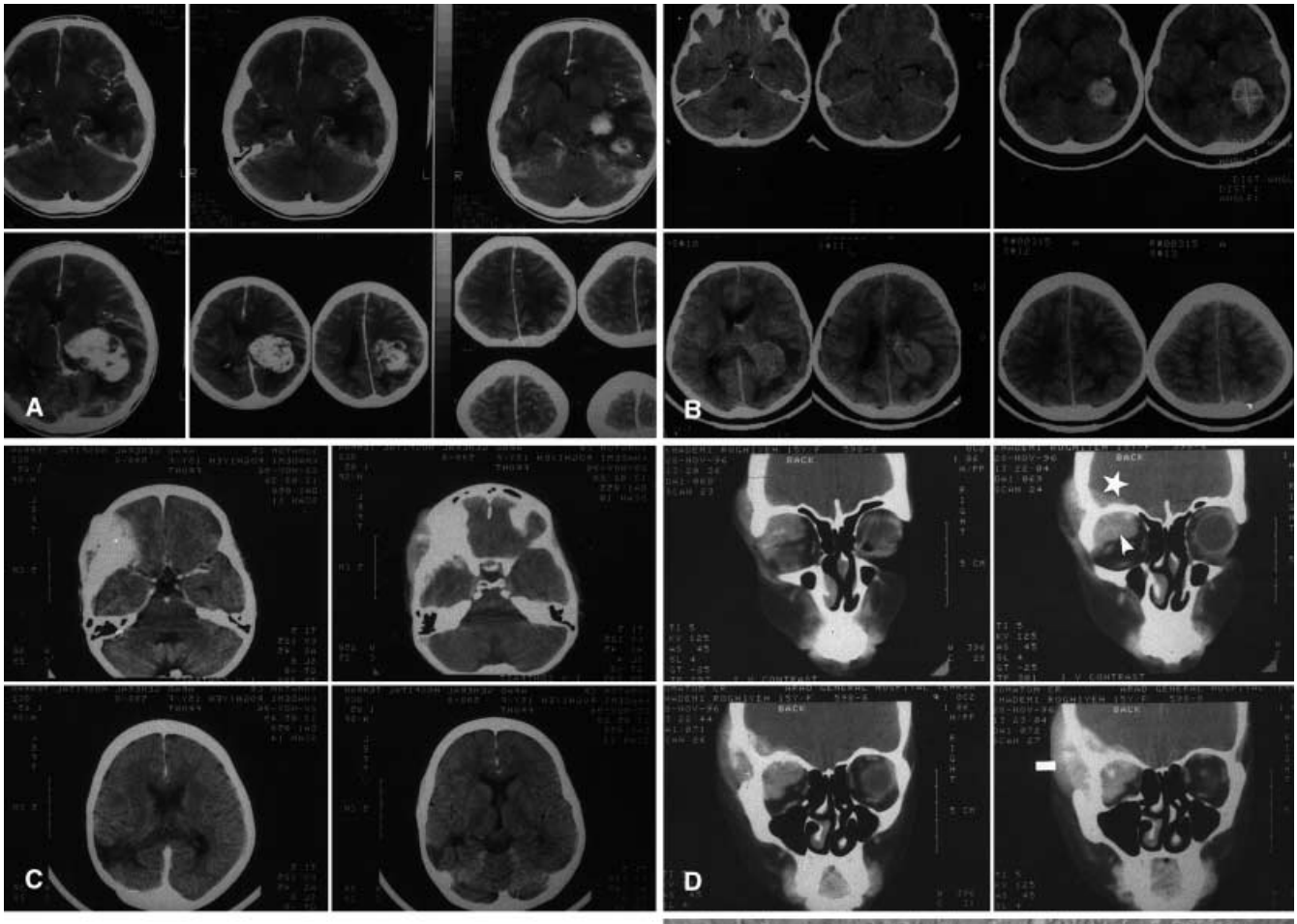



**Fig. 2** **A** CT performed at first admission, showing obstructive hydrocephalus resulting from a nonhomogeneously enhancing lesion in the IV ventricle. **B** Contrast-enhanced CT scan performed on second admission, showing a larger nonhomogeneously enhancing lesion in the left frontoparietal region (*black arrow*) and a smaller enhancing lesion (*white arrow*) in the right parietal cortex. **C**, **D** MRI performed on second admission, revealing the nonhomogeneous lesion in the left frontoparietal region in the axial T2-weighted images with hyperintensity in the periphery (hemosiderin ring) and hypointensity in the center, while in the T1-weighted sagittal images the lesion appears mainly hyperintense (*black arrow tip*). There is no sign of recurrence of the tumor in the posterior fossa region. **E** Contrast-enhanced CT scan performed after the second operation, revealing the low-density area at the site of the resected cavernoma. **F** Histopathological features of the laminated wall of the thrombosed vascular channel containing both fibrotic and gliotic tissues. H&E , ×130

port was 'meningotheliomatous meningioma' with no mitotic figures or any stigmata compatible with invasiveness or malignant behavior of the tumor (Fig. 1C). Control MRI after 18 months did not show any tumor residue or recurrence. The girl gained full power in the extremities and attended high school again. Forty months later, she presented with headache nausea and vomiting. Physical examination revealed that the patient was left hemiparetic with bilateral papilledema. Contrast-enhanced MRI showed an infiltrative intra-axial lesion filling up the III ventricle and possibly extending along the fornices towards the medial occipital regions (Fig. 1D) bilaterally. A right frontal craniotomy and transventricular approach to the III ventricle was performed, and a purplish gray soft and moderately hemorrhagic tumor filling up the III ventricle was removed as far as possible. This tumor turned out to be a grade 4 astrocytoma. The left hemiparesis worsened after this intervention but has been improving, and a course of combined chemotherapy and cranial radiotherapy consisting of 2000 cGy radiation is planned.

Case 2

This boy was admitted at the age of 7 years complaining of vertigo and dizziness of several weeks' duration. Positive findings at the time of admission were: bilateral papilledema and severe truncal ataxia. CT scanning (Fig. 2A) showed a rather homogeneously enhancing posterior fossa midline tumor obstructing the IV ventricle and associated supratentorial ventricular dilatation. The tumor was excised subtotally and a ventriculoperitoneal shunt was installed. The pathology report specified ependymoma. Postoperative radiotherapy included a total dose of 5400R to the whole brain, the tumor bed and the spinal axis. The patient remained clinically well, and two subsequent CT scans performed during the following 4 years did not show any local tumor recurrence. He developed at-



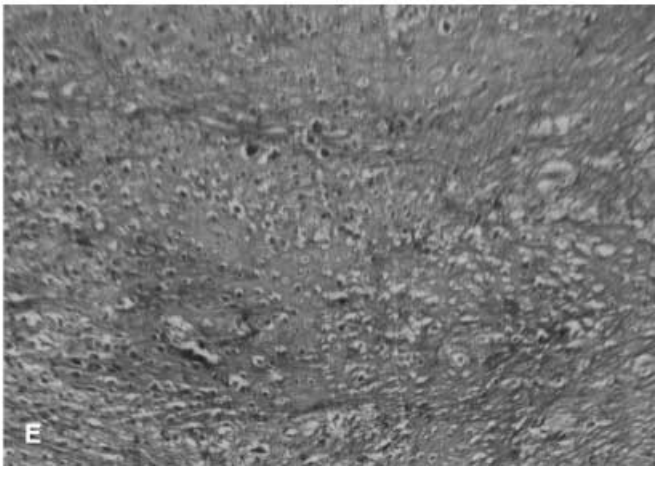




**Fig. 3 A** Contrast-enhanced CT scan performed before the first intervention, showing a nonhomogeneously enhancing lesion in the left posterior parietal region, which was excised, gross total resection being attained. **B** Contrast-enhanced CT performed after 1 year, revealing tumor recurrence in situ. This lesion was also removed, and postoperative radiation was delivered. **C**, **D** Axial and coronal CT scans performed after 28 months when the patient presented with headache and rapidly progressing unilateral exophthalmos. It shows an enhancing lesion extending within the orbit (*white triangle*), intracranially within the anterior and midfossa regions (*white star*) and extracranially in the subtemporal region (*small white rectangle*). **E** Histological features, showing a mosaic pattern of packed cellular aggregates with rather palisading arrangements. There are light blue islands of chondroblastic and pinkish areas of osteoid differentiation. H&E, ×190

tacks of epilepsy 9 years later at the age of 16, followed by right-sided hemiparesis. CT scanning (Fig. 2B) and MRI (Fig. 2C, D) showed (a) no tumor recurrence at the site of the primary lesion, (b) at least two supratentorial lesions. The larger lesion was located in the deep left posterior paraventricular region; it was relatively round and enhanced moderately after contrast material injection in CT scanning. This lesion was nonhomogeneously hypointense in T1-weighted and hyperintense in T2-weighted images, containing flow-void regions within it. The lesion was resected through a trans-sulcal, high posterior parietal approach. It was a large, thick-walled cyst filled with partially thrombosed vessels and dark brownish fluid. The patient's right hemiparesis worsened, and he became severely dysphasic postoperatively, with a gradual and remarkable recovery of function afterwards. The smaller lesion in the right parietal cortex is being monitored with serial MRI (Fig. 2E). The histopathological diagnosis was cavernous angioma (Fig. 2F).

Case 3

This 15-year-old girl had an ependymoma of the left posterior temporo-parietal region resected totally at the age of 11 years

(Fig. 3A). The family refused radiation therapy and the tumor recurred in the same place after 1 year (Fig. 3B). It was excised through the previous approach, and this time a total dose of 5400 R of whole-brain irradiation was delivered. Follow-up CT scans did not show any local tumor recurrence for the next 28 months. At this time, the girl presented with a painful left unilateral exophthalmos, which was rapidly progressive . Her vision was declining rapidly, and a tumor mass became palpable in the temporal and zygomatic regions. CT scanning (Fig. 3C, D) revealed a multicompartmental tripod lesion presenting in the orbit, intracranially in the subfrontal and temporal fossa regions and extracranially in the subtemporal region. The tumor was approached through a lateral orbitotomy ('Kronlein' approach), and the arch of the zygoma was removed. The bone of the pterion and the lateral wall of the orbit had been infiltrated and destroyed by a meaty and cartilaginous purplish gray, moderately hemorrhagic tumor. The tumor was removed from the orbit and subtemporal cavities. The involved parts of the dura of the anterior temporal and subfrontal regions were excised, and the gross total excision of the tumor masses presenting both intra- and extradurally was carried out. There was no tumor invasion into the adjacent cortex of the brain. The dura was repaired with temporalis fascia, and the arch of the zygoma was replaced and fixed. The diagnosis noted in the pathology report was 'Chondrosarcoma' (Fig. 3E). The exophthalmos subsided postoperatively, and the patient was transferred to the oncology department, receiving systemic chemotherapy and local radiotherapy. Unfortunately, the tumor recurred rapidly after 3 months, with the tumor mass extending widely both intra- and extracranially, leading to her death.

## Discussion

Irradiation of the CNS undertaken as an integral part of the treatment and management of intracranial tumors has adverse effects, which can be divided into three groups according to the time of appearance. These are: (a) 'acute reactions,' occurring during the course of irradiation, (b) 'early delayed reactions,' probably a result of demyelination but usually transient and disappearing spontaneously within few months, and (c) 'late delayed reactions' occurring several months to several years later and constituting the major hazards of radiation therapy for brain, spinal cord and adjacent tissues [6]. These late delayed complications can be divided into two categories; (1) tumors leading to presentation with the symptoms of radiation necrosis, (2) secondary radiation-induced tumors of the brain and its adnexae [2, 5, 6, 7, 16, 27, 29, 31,43, 45]. The tumorigenic effect of ionizing radiation was mentioned as early as 1902 by Frieben [12] and emphasized later by Margulis et al. [24] . Even though the relative risk of developing a new tumor of any kind after cranial radiotherapy is <1%, it can induce a low but life-long risk for occurrence of a new tumor, with a relative risk of 1.8 per 10,000 persons per year [58]. According to the report from Mount Sinai Hospital [23], the tumor–dose relationship can be categorized on the basis of the amount of radiation delivered, i.e. (1) low dose <1000R; (2) moderate or medium dose 2000>R>1000, and (3) high dose >2000R [2, 3, 6, 16, 33, 36, 39, 44]. The therapeutic irradiation of the scalp according to the 'Adamson-Kienbock technique' [1] was used for years to treat ringworm infestation of the scalp, i.e. tinia capitis, before proper antifungals became available. In this technique, about 140R is absorbed by the brain [1]. The occurrence of soft tissue tumors in such field of low-dose irradiation (LDRI) has also been emphasized by other authors [50, 52, 53] reporting the development of tumors of the skull bone and neck after exposure to full-mouth diagnostic dental X-ray film [3] and to irradiation for enlarged tonsils [54] and thymus [55]. The most common neoplasms occurring in this series of low-dose radiation-induced tumors (LDRIT) are meningiomas [3, 9, 23–25, 46, 58]. RIMs can occur intracranially [3, 39], extracranially [24, 33, 35] and intraspinally [23, 41]. In 1953, Mann et al. reported the first case of suspected RIM in a 4-year-old girl who had received 6500R irradiation to the orbit for the treatment of an optic nerve glioma [32]. Our search of MEDLINE revealed about 312 reported cases of radiogenic meningiomas. Among them, only 123 cases of well-documented LDRI intracranial meningiomas can be distinguished, which amount to 2.3–21.4% of all cases of meningioma operated on in several departments [3, 23, 36, 56]. In our own experience (unpublished data), LDRIMs comprise 21.7% of cases of meningiomas operated on by us during the last 18 years. According to our search, there are 122 cases of documented high-dose radiation-induced (HDRI) meningiomas reported in the literature [7, 23, 32, 36, 48, 50, 58, 59]. Among all the reported cases, we did not encounter a low-, medium- or high-dose radiation-induced spinal meningioma occurring in childhood and adolescence. The anecdotal reports of radiogenic meningioma of the spine are quoted from the Russian literature [41] and in a 75-year-old lady several years after irradiation for keloids of the skin [23]. Interestingly, there is a single case report of three different RITs occurring within the field of irradiation in the same time period. The tumors were ependymoma in the right caudate nucleus, cavernoma in the left frontal region, and a temporal meningioma [2]. The interesting point in our patient with multiple RITs is that the second RIT was a glioma, which occurred 4 years after successful treatment of the first RIT, which was a cervical meningioma.

According to the literature [11], the following features are characteristic of RIT or at least justify considering whether a secondary lesion is an RIT. The new tumor occurs in the irradiation field and appears after a latent period, which is usually more than years or decades. It occurs with sufficiently high frequency to suggest a causal relationship. The histopathology of the second tumor is different from that of the neoplasm initially treated. The secondary tumor can be experimentally induced in animal models and may have a higher incidence of occurrence in irradiated individuals than in control groups [6, 11]. There may also be a positive correlation between the radiation dose and the incidence of occurrence of the

secondary tumor [6]. In light of these criteria, it is conceivable that in the cases that are the subjects of our present report the occurrence of these five rare lesions as secondary tumors is not merely coincidental and should be regarded as radiogenic lesions. We may suggest that in rare situations, and especially when radiation has been delivered in childhood, there may be a shorter time interval before development of a secondary and RIT [12, 29].

The average age of presentation of RIMs is 32.3 years for high-dose and 46 years for low-dose radiation-induced meningiomas [3, 36]. To our knowledge, only 15 cases of intracranial RIMs presenting in patients under the age of 18 have been reported in the literature [24, 33, 36, 44, 46]. The latent periods quoted on the basis of the meta-analysis performed by Musa et al. in 1995 are 20 years for HDRIMs and 32 years for LDRIMs [24, 26, 33, 36, 38, 60]. In our case of spinal meningioma, the time interval was only 14 years. Regarding the salient clinicopathological characteristics of RIMs, i.e. their multiplicity, pleomorphism, local invasiveness and high rate of occurrence [57], not one of these features was present in this case of spinal RIM, making it unique.

Several theories have been postulated to describe the mechanism of occurrence of radiogenic tumors: (a) radiation can initiate genetic alterations by disrupting the deoxyribonucleic acid (DNA) of specific chromosomes, such as chromosome 22 [6, 12] or p53 tumor suppressor gene [12] or unmasking a previously suppressed oncogenic genetic material [17], (b) karyotypic instability due to radiation-induced multiple chromosome aberrations may be responsible [18]. As we learn more about the genetic aspects of RIMs and RI sarcomas, such hypotheses as these could be further investigated, but other possibilities might also be considered: (c) The preferential effect of radiation on the tissue microenvironment, permitting growth of pre-existing malignant cells [12]; (d) miscellaneous factors such as adjunct chemotherapy, underlying disease, radiation type and dose and patient's age [27, 31]; (e) vascular parenchymal alterations leading to necrosis and impairment of cerebral microcirculation, release of platelet-derived and vascular endothelial growth factors [19], beta chain of fibroblast growth factor [47, 49, 61], and raised tissue level of basic fibroblast growth factor [31], and (f) radiation-induced genetic predisposition in chromosomes 7q and 11.2-q21 [17, 21].

The multifactorial origin of cavernous malformations is likely, and genetic causes, cranial irradiation [15, 17], viral causes and de novo formation have all been mentioned [13, 14]. Our review of the literature on radiation-induced cerebral occult vascular malformations (OVM) revealed reports of 21 cases of cerebral OVM including cases of cavernoma and telangiectasias [2, 13, 15, 20, 29, 42, 44, 61]. These patients had all been treated previously with moderate- or high-dose radiation, and the time interval varied from 18 months to 23 years [13, 29, 61]. In our case, the cavernoma became symptomatic 9 years after preventive irradiation of whole brain for ependymoma of the IV ventricle. Interestingly enough, the time intervals for development of RI vascular neoformations or RI vascular tumors are noticeably shorter than that required for development of other benign RI tumors [13, 29]. However, bearing in mind that some authors may still remain skeptical about cavernomas as a possible RIT or radiation-associated lesion, we would like to add this case to those reported in the literature, to support this possibility. It may be possible to perform a meta-analysis involving all reported cases and reach a statistically significant value to support the hypothesis.

Regarding sarcomas, even shorter intervals have been mentioned in animal experiments on radiation-induced tumors, e.g. 15 months for the development of fibrosarcoma in monkeys [25] The incidence of occurrence of sarcomas in the CNS is very low, i.e. 1–2.5% of all primary intracranial tumors. Our case is probably the second reported of a chondrosarcoma arising 3 years after irradiation for a temporal lobe ependymoma. This reminds us that such a rare but devastating complication of therapeutic irradiation may occur sooner after radiation than is generally perceived.

Even though there is a seven-fold increase in the risk (95% confidence interval) of occurrence of RITs of the CNS over a period of 30 years of follow-up [5], it is conceivable that all these second tumors could have arisen spontaneously. Consequently, an assessment of the genetic make-up of these tumors is necessary in future studies.

## Conclusion

In the light of the findings in this series of rare cases, it appears reasonable to anticipate an increased incidence of radiation-associated tumors (RITs) and/or RI vascular malformations in younger patients who have previously undergone irradiation for malignant tumors within a short interval. In light of the fact that improvements in surgical and other adjunctive treatments may lead to longer overall survival and a longer disease-free period, the incidence of such RITs will increase. Whenever radiation is administered to very young children, serial screening studies are suggested to enable earlier detection and treatment of possible secondary RITs. It should be borne in mind that the second tumor may turn out to be a benign lesion.

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