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## Radiotherapy-induced secondary cranial neoplasms in children

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**Abstract** *Background:* Secondary malignant neoplasms (SMN) in CNS tumor survivors has become problem of increasing concern over the last 20 years. These tumors usually occur in a different site from the primary brain tumor several years after treatment. *Case report:* We report secondary cranial malignant neoplasms in three patients who were treated with irradiation and chemotherapy for their primary brain tumors. The first case is a male survivor of an orbital rhabdomyosarcoma who developed a meningioma 8 years later. The other two cases are female survivors of ependymomas who were irradiated at the age of 3 and developed secondary gliomas 8 and 17 years after therapy respectively. *Conclusion:* Patients carry a risk of developing SMNs many years later since irradiation is still an important

part of the treatment. An SMN may have a benign course, as in meningioma, or be a dilemma for the patient, as in glioblastoma.

**Keywords** Secondary malignancy · Meningioma · Brain tumor

### Introduction

One of the most serious delayed consequences of cancer therapy in the survivors of childhood cancer is the development of second malignant neoplasms (SMN). Among patients treated with cranial irradiation for primary cancer there is strong evidence to suggest that radiotherapy may be associated with secondary brain tumors [1, 12]. As demonstrated in a large pediatric series of acute lymphoblastic leukemia, the risk of developing a secondary brain tumor was higher among the children who received cranial irradiation and was also higher among those who were under 5 years of age [8]. Mostly meningiomas, but also malignant brain tumors,

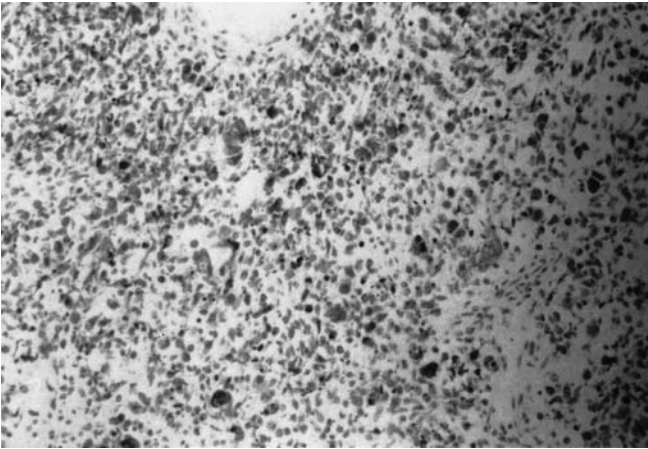
to a lesser extent, have been reported in the literature to occur in children and adolescents exposed to high-dose irradiation [3, 4, 7, 10].

We report three children who developed a meningioma or malignant brain tumor many years after completion of therapy for their primary tumors.

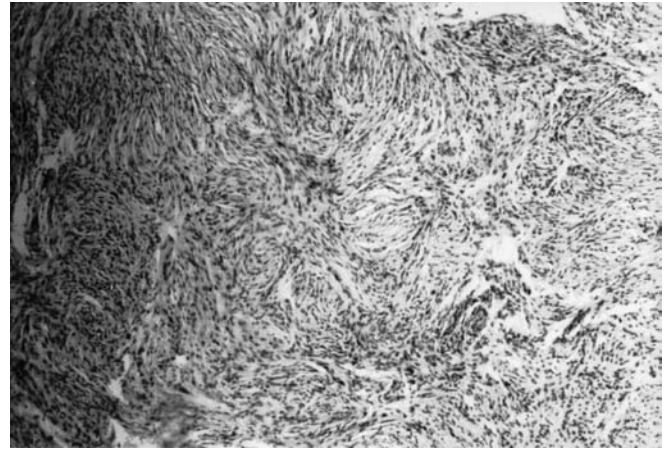
### Case reports

#### Patient 1

A 7-year-old boy presented in March 1989 with blurring of vision and swelling on the right eye. Physical examination showed a right-sided orbital mass. Computerized tomography of this region revealed a mass located between the retrobulbar space and the lat-



**Fig. 1** Patient 1. Rhabdomyosarcoma, desmin immunoreactivity in the tumor cells (Strept-Avidin, fast red,  $\times 20$ )



**Fig. 2** Patient 1. Second tumor. Atypical meningioma, focally increased cellularity (H&E,  $\times 20$ )

eral wall of the orbita. A biopsy confirmed the diagnosis of embryonal-type rhabdomyosarcoma.

**Histopathological findings.** The tumor was composed of an admixture of undifferentiated cells and elongated strap cells. Some small round cells possessed eccentric eosinophilic cytoplasm. Periodic acid-Schiff (PAS) positive tumor cells were seen. On immunohistochemical evaluation, positive staining of neoplastic cells with antibodies against vimentin, desmin, and muscle-specific actin were noted, whereas S-100 and EMA were not immunoreactive in the tumor cells (Fig. 1).

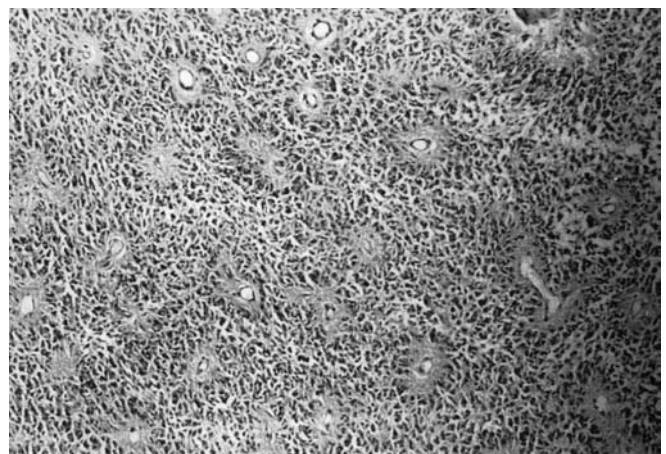
No other tumor site besides the primary site was found during the evaluation of staging. The patient was designated clinical stage II. He underwent right orbital exenteration and was treated with vincristine, actinomycin-D, cyclophosphamide, and adriamycin. He was then given local radiation therapy (5,000 cGy). The patient was disease-free until November 1997 when another orbital mass occurred. He developed vomiting and headache. On physical examination the tumor was palpable (3 $\times$ 2 cm in diameter) under the skin flap that covers the orbital opening. Diagnostic imaging studies revealed a mass extending from the right orbita through the ethmoid cellulae, sphenoid sinus, medial orbital wall, and frontal lobe of the brain. The tumor was near-totally resected and diagnosed as an atypical meningioma.

**Histopathological findings of the second tumor.** The tumor cells were spindle-shaped with oval nuclei and delicate chromatin pattern. Parallel and interlacing bundles of cells were prominent and whorl formations were infrequent (Fig. 2). The tumor had the features of a fibrous meningioma but there were foci of increased cellularity, minimal necrosis, and four mitotic figures per ten high-power fields. Diffuse immunoreactivity with vimentin and focal immunoreactivity with EMA were observed in the tumor cells. The mean Ki-67 value was 9%. The tumor cells showed focal immunoreactivity to progesterone receptor.

The rest of the tumor grew slowly over a 10-month-period after which it was totally resected in a second operation. The patient is still disease-free after 22 months.

#### Patient 2

A 3-year-old girl presented in 1989 with headache, lethargy, and vomiting, which she had had for a month. On physical examination she was found to have a bilateral papilledema and abnormal

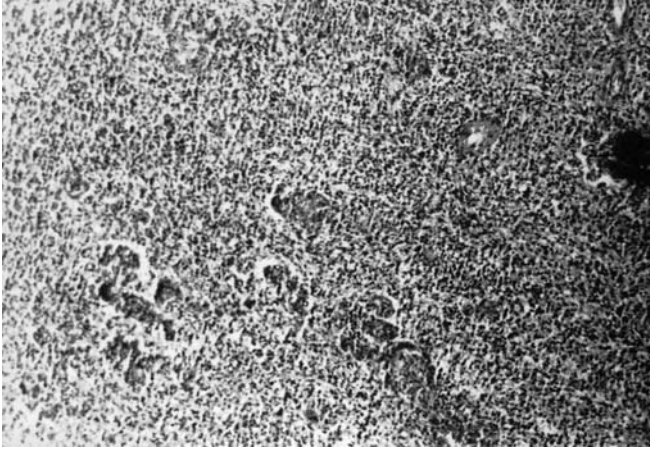


**Fig. 3** Patient 2. Ependymoma, prominent perivascular pseudorosettes (H&E,  $\times 20$ )

gait. Computerized brain tomography revealed a cerebellar mass in the fourth ventricle. The tumor was totally removed and diagnosed as a low-grade ependymoma.

**Histopathological findings.** The tumor was composed of monotonous, monomorphic cells with round to oval nuclei, which contained dense chromatin material. At low magnification, there were perivascular pseudorosettes consisting of delicate cytoplasmic processes terminating on the vessels. True ependymal rosettes were not seen; however, some nuclei were attempting to simulate rosettes (Fig. 3). Glial fibrillary acidic protein (GFAP) was immunoreactive in the tumor cells.

The patient was treated with radiation therapy alone (5,400 cGy). In 1997, she presented with headache, blurred vision, and somnolence, which she had had for a week. The patient had dysarthria, somnolence, abnormal gait, and left homonymous hemianopsia on physical examination. Radiologic imaging showed a mass located on the right deep temporal lobe. However, the cerebellum was atrophic and calcified and the first tumor site was gliotic on magnetic resonance imaging. The tumor was subtotally resected. The histopathology was that of a glioblastoma multiforme.



**Fig. 4** Patient 2. Second tumor. Glioblastoma multiforme, small anaplastic cells and vascular endothelial proliferations (H&E  $\times 20$ )

*Histopathological findings of the second tumor.* The highly cellular tumor was composed of predominantly small anaplastic cells with darkly stained nuclei. Vascular proliferation was seen throughout the lesion (Fig. 4). There were large necrotic areas. The cells showed focal immunoreactivity to GFAP and no reactivity to leukocyte common antigen (LCA) and synaptophysin. Proliferative activity was prominent with numerous mitoses. The growth fraction, as determined by the antibodies Ki67/MIB-1, showed a mean value of 55%. P53 (DO-7) protein immunoreactivity was 74%.

The patient was given three courses of cisplatin plus etoposide followed by eight courses of vincristine plus cyclophosphamide. Nevertheless, her neurological and radiological findings progressed after eight courses of chemotherapy and she died.

#### Patient 3

This 19-year-old woman had initially presented in 1982, at the age of 3 years, with headache and vomiting. She had bilateral papilledema and right upper arm weakness. A carotid angiogram revealed a left frontal mass. She underwent a frontal craniotomy for cyst drainage and the biopsy of this mass revealed it was a papillary ependymoma.

*Histopathological findings.* At low magnification, the tumor had a pseudopapillary growth pattern in which vessels were covered by multiple layers of the tumor cells with round to oval nuclei. In the solid areas, there was conspicuous cellularity, with fewer pseudorosettes. Endothelial proliferation, necrosis, and mitotic activity were absent. The tumor cells showed immunoreactivity to GFAP.

She received total cranial irradiation (59 Gy) and chemotherapy (CCNU). She did well until 1999, when she presented with left hemiparesis and recurrent partial seizures. Cranial MRI revealed a right parietal mass. She underwent a right parietal near-total tumor resection. The histopathology was that of a glioblastoma multiforme.

*Histopathological findings of the second tumor.* There were areas that had different degrees of cellularity. Highly cellular areas were predominantly composed of small anaplastic cells. Vascular proliferations forming "glomerular tufts", necrosis, and numerous mitoses were also seen. Immunoreactivity with GFAP was focal in the tumor cells. The mean Ki67 and p53 values in the tumor tissue were found to be 17% and 70% respectively.

The patient was given fotemustine chemotherapy and four courses of this chemotherapy achieved stable disease. Thereafter, she progressed and died.

## Discussion

For many years it has been known that meningiomas and brain tumors may occur following high-dose cranial irradiation [4, 9, 10]. The number of brain tumors among patients who had received cranial irradiation was reported to be nearly 27 times greater than expected, whereas no such tumors were seen after chemotherapy [10].

Heyn et al. [5] reported that the development of an SMN (mostly bone sarcoma and ANLL) after treatment for a rhabdomyosarcoma was higher in patients who had received chemotherapy of alkylating agents and radiotherapy than in those who received only one of these therapeutic modalities. The latency period of developing meningioma can be as long as 36 years after treatment [2, 3]. Meningiomas after high dose radiation in children are mostly benign and complete removal is possible in most cases [4]. The presented atypical meningioma case that occurred 8 years after chemotherapy with alkylating agent and orbital irradiation, had a benign course for 22 months. Atypical meningiomas have high recurrence rates. In an adult series, tumor recurrence was reported in 62.5% of the patients with orbital meningiomas [6]. In our case, gross total tumor resection was considered to be predictive of delayed recurrence.

Radiation-induced gliomas were reported after treatment for primary brain tumors and several types of childhood cancers (ALL, retinoblastoma, NHL, craniopharyngioma, histiocytosis, teratoma, etc.) [9, 11, 13, 14]. There were two radiation-associated glial tumors reported after 5 and 14 years of radiotherapy for ependymoma in the current literature [14]. In our series, two female patients developed secondary malignant gliomas that occurred in different sites from the primary site. The latency periods of SMN were 8 and 17 years after treatment. These two children had been irradiated at the age of 3. This may indicate, again, that children are at an increased risk of developing secondary cranial neoplasms when irradiated under the age of 5 [8]. Unfortunately, they had no chance of having cranial irradiation again and they did not respond to chemotherapy after the surgical resection of the tumors.

## Conclusion

Our experience with three second malignancies of the brain, as well as that of other authors, suggests that long-term survivors of childhood cancer who have previously received cranial irradiation are at risk of SMN and should be followed-up for a long period.

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