

## Radiation-induced adult medulloblastoma: a two-case report and review of the literature

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**Abstract** Radiation-induced medulloblastoma is an exceedingly rare phenomenon for which treatment standards have not been established. The literature suggests that these tumors are high grade with aggressive behavior. We report two cases of radiation-induced medulloblastoma which have been treated with full dose re-irradiation with curative intent. In both cases, treatment toxicity and tumor progression proved to be insurmountable obstacles. Further reports are necessary in order to fully characterize this clinical entity so that more effective therapies may be sought.

**Keywords** Radiation-induced malignancy ·  
Medulloblastoma · Re-irradiation

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### Introduction

Medulloblastoma is a rare tumor that accounts for only about 1% of adult CNS tumors [1]. The treatment paradigm for adult medulloblastoma includes maximal safe resection, radiation therapy, and possibly chemotherapy. Radiation-induced medulloblastoma poses a more difficult therapeutic dilemma because the surrounding normal brain tissues have often received a full course of radiotherapy. With radiation-induced tumors of other histologies, there is evidence that being radiation-induced may portend a more aggressive biology than the non-radiation-induced variants. With sufficient latency between the prior radiotherapy and the radiation-induced medulloblastoma, definitive surgery, radiotherapy, and possibly chemotherapy may be considered therapeutic options. We report two cases of radiation-induced medulloblastoma that occurred several decades after adjuvant full-dose radiotherapy for craniopharyngioma and low-grade astrocytoma.

### Case report 1

The first patient was a 44-year-old woman who had been diagnosed with craniopharyngioma at the age of 11 years in 1975. Her original tumor was treated at our institution with maximal safe resection followed by adjuvant radiation therapy to a total dose of 5,500 cGy. She remained disease free for over three decades subsequent to her treatment, though she did develop a moderately shortened stature, as well as panhypopituitarism and diabetes insipidus that were controlled medically. Her last routine follow-up scan was performed in 2006, and revealed no evidence of tumor recurrence. The patient was able to live independently with her husband, and maintained a good quality of life until

2008 when she experienced progressive difficulty with her gait. She subsequently developed memory loss and somnolence. She sought medical attention with her primary care physician who ordered an MRI scan of the brain. It revealed a heterogeneously enhancing mass involving the left cerebral peduncle, the cerebellum, and the pons (Fig. 1a). The patient was referred back to our institution for stereotactic biopsy.

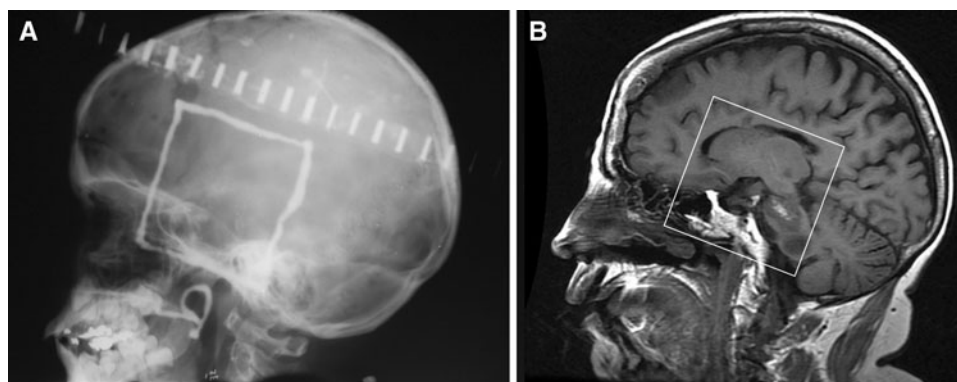
Pathology revealed WHO grade IV anaplastic medulloblastoma that was characterized by dense cellularity, marked nuclear pleomorphism, nuclear molding, brisk mitotic activity, and abundant apoptotic cell death (Fig. 2a). Many of the tumor cells also displayed intranuclear cytoplasmic pseudo-inclusions. Immunohistochemistry revealed strong and diffuse staining for synaptophysin and microtubule-associated protein 2 (MAP-2), with negative staining for glial fibrillary acidic protein (GFAP), S100 protein, and low molecular weight cytokeratin (Fig. 2b, c; negative stains not shown).

Staging of the neuraxis including MRI of the total spine and CSF cytology were both negative. As the mass involved the brainstem, it was deemed unresectable. As such, she underwent definitive radiotherapy including craniospinal irradiation to a dose of 36 Gy. The gross

tumor with margin received a boost dose to 54 Gy using intensity modulated radiation therapy. Of note, a planning MRI scan done 2 weeks after original diagnostic scan revealed interval tumor progression both at the predominant mass, as well as within the biopsy tract (Fig. 3). The patient tolerated the course of radiotherapy with some difficulty, requiring hospital admission for hypovolemia. After completion of treatment, she experienced an acute decline in mental status and was found on examination to have an unreactive pupil. Repeat MRI revealed no evidence of hydrocephalus, herniation or significant tumor progression. The patient failed to respond to both a trial of steroids and empiric antibiotics for a possible underlying infection. Her family ultimately placed her in hospice care 1 month later and she died shortly thereafter.

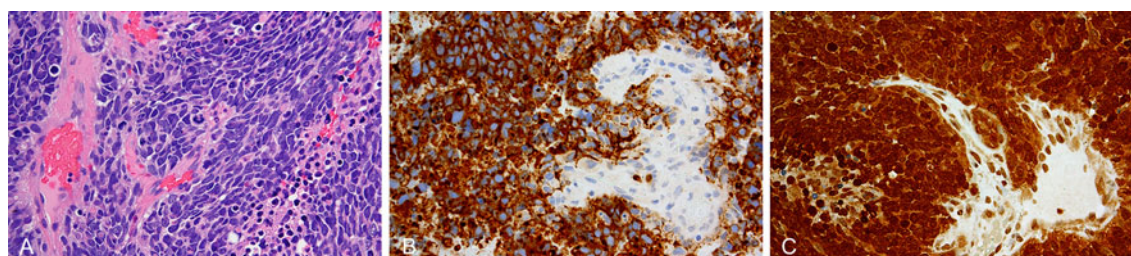
## Case report 2

The patient was a 46-year-old woman who was diagnosed with a pilocytic astrocytoma at the age of 5 years. She was treated at an outside institution with surgery, shunt placement, and adjuvant radiotherapy to a dose of 2,400 cGy. She was disease free until the age of 20 when she



**Fig. 1** **a** Lateral plain film X-ray showing the original RT portal for the adjuvant treatment of a subtotaly resected craniopharyngioma. **b** Sagittal MRI, Fluid Attenuated Inversion Recovery (FLAIR) sequence showing the secondary medulloblastoma to be in the high

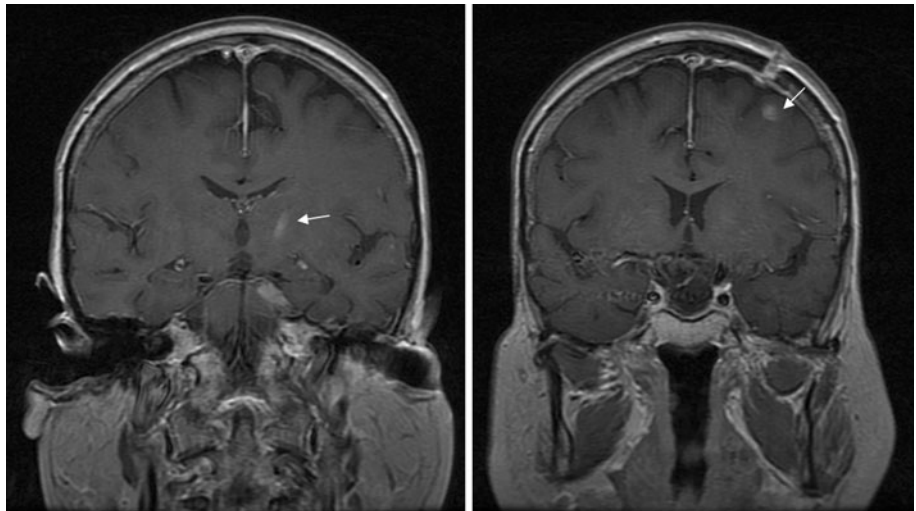
dose region of the previous RT field. An estimation of the previous RT field is superimposed onto the current MRI



**Fig. 2** **a** Anaplastic medulloblastoma (Case 1) demonstrating dense cellularity, marked nuclear pleomorphism, nuclear molding, and a brisk mitotic rate (H&E,  $\times 400$ ). **b** Immunohistochemical stain for

synaptophysin showing strong cytoplasmic immunoreactivity ( $\times 400$ ). **c** Immunohistochemical stain for MAP-2 showing strong cytoplasmic and nuclear immunoreactivity ( $\times 400$ )

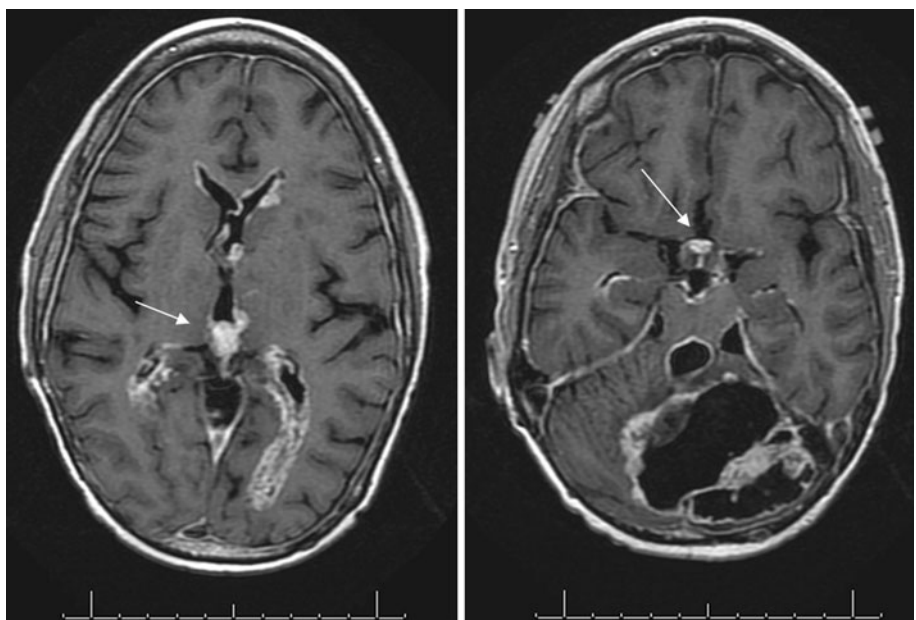
**Fig. 3** Coronal MRI, contrast-enhanced FLAIR sequence showing the RT-induced medulloblastoma. This set of images was taken as part of RT-planning, occurring approximately 3 weeks after the original diagnostic MRI. In this time interval, the tumor appeared to seed the biopsy tract, as seen with the enhancing nodularity at the left vertex



experienced a recurrence of the astrocytoma. She underwent repeat resection without further adjuvant therapy. The surgical pathology was again consistent with grade I astrocytoma. Post-operatively, the patient experienced only mild ataxia, but otherwise maintained an excellent performance status. She married and was able to work full-time and raise two children. She remained healthy until 2008, when she experienced a worsening of her ataxia and a progressive short-term memory loss. MRI of the brain demonstrated a multilocular cystic mass in the left posterior fossa with nodular enhancement associated with septations on the walls of the lateral ventricles, as well as diffuse ventriculomegaly (Fig. 4). The patient subsequently underwent a biopsy with pathology demonstrating WHO grade IV anaplastic medulloblastoma. She underwent an MRI of the entire spine, which revealed diffuse

leptomeningeal dissemination. She was then referred to our institution for therapy. Incidentally, a planning MRI of the brain performed 1 month after the initial diagnostic scan demonstrated progression of dural and ependymal disease as well as enlarging lesions within the pituitary region, pineal region and posterior aspect of the medulla. The patient went on to receive craniospinal irradiation to 4,050 cGy at 150 cGy per fraction. Her gross brain disease received a boost, bringing the total dose to 5,490 cGy. She initially tolerated her therapy well, but experienced a precipitous decline in performance status and mental status during the final week of radiotherapy. Imaging revealed persistent hydrocephalus. After completion of radiotherapy, the patient underwent a shunt revision, but the hydrocephalus was intractable. Her mental status continued to deteriorate and her family placed her into hospice care

**Fig. 4** Axial post-contrast T1 FLAIR weighted images demonstrate a cystic posterior fossa mass with peripheral nodular enhancement. These also illustrate diffuse dural and ependymal enhancement with more focal enhancing masses in the pineal region and optic chiasm (arrows)



where she subsequently died, 2 weeks after completion of radiotherapy.

## Discussion

Mutations in genes in the Sonic HedgeHog-Patched pathway appear to predispose to medulloblastoma development [2, 3]. A preclinical model of radiation-induced medulloblastoma in mice has been published recently [4]. In this report, the authors irradiated mice that were heterozygotes for a *Ptc1* gene mutation. These mice developed medulloblastoma whereas the non-irradiated controls developed only abnormal cerebellar proliferations. It is hypothesized that the radiotherapy provides the “second hit” genetically in these mice. Moreover, this hypothesis provides a possible mechanism for radiation-induced medulloblastoma in humans. A series of radiation-induced gliomas has been described in which the genetic mutations observed were found to be similar to those seen in spontaneous gliomas [5].

Radiation-induced medulloblastoma is an exceedingly rare disease entity, with only two cases previously reported in the literature. Radiation-induced medulloblastoma is likely related to radiation-induced primitive neuroectodermal tumors (PNET), of which there have been seventeen cases previously reported [6–8]. More common radiation-induced brain tumors include meningioma and glioma. In spite of radiation-induced glioma being a more common entity than radiation-induced medulloblastoma, a recent review of radiation-induced glioma has cited only 116 reported cases in the world literature [9]. As such, radiation-induced medulloblastoma may be rare because of the fact that adult medulloblastoma or PNET represents a smaller fraction of adult brain tumors than glioma.

The first reported case of radiation-induced medulloblastoma occurred in a patient who was 15 years subsequent to cranial irradiation for low grade astrocytoma [10]. The medulloblastoma developed in the temporal lobe contralateral to that of the glioma. The second report occurred in a patient who had a pineal germinoma at the age of 20 [11]. This patient was treated with definitive radiotherapy to a dose of 45 Gy, and remained disease free for 8 years until he developed the secondary medulloblastoma adjacent to the high dose treatment volume. Both of the cases reported herein involve patients who experienced the secondary tumor in the high dose region of the previous treatment field. In fact, in one of the patients, the simulation films from the initial treatment fields were still available (Fig. 1a).

Both of the previous cases of radiation-induced medulloblastoma in the literature were of high-grade large cell histology. Both of our cases likewise had high-grade large cell histology. Anaplastic large cell medulloblastoma is an

entity which has been characterized by large rounded nuclei, prominent nucleoli, and high mitotic rates [3]. Furthermore, immunohistochemical staining generally shows synaptophysin immunoreactivity [12]. More recent data suggests that genomic aberrations such as *MYC* and *MYCN* amplifications can also have prognostic value [13]. While *MYC* levels were not obtained in the current specimens, both patients in this report showed classic evidence of diffuse synaptophysin immunostaining, as well as the aforementioned pathologic hallmarks of anaplastic medulloblastoma.

Though the data are sparse, radiation-induced medulloblastoma appears to be a very aggressive tumor. Most patients in the literature with radiation-induced PNET or medulloblastoma have fared poorly with reported median survival times of only 12 months [6]. In our first patient, the tumor had already seeded the biopsy tract in the interval between the biopsy and the MRI done for radiation planning. In the second patient, there was also evidence of tumor progression in the 1 month interval between the patient’s first diagnostic scan and the planning scan for radiation therapy.

It should be noted that only one of the previously reported patients with radiation-induced PNET or medulloblastoma received re-irradiation with curative intent. Most patients had been previously treated with full dose radiotherapy, posing a difficult therapeutic dilemma regarding the lifetime tolerance of the brain to radiotherapy. In the prior case reports, most radiation-induced PNET or medulloblastoma were treated with craniotomy with tumor resection if possible and chemotherapy consisting of CCNU and/or PCV [6]. Others were treated with palliative intent given a poor performance status at presentation [11]. Our intent with the two patients reported herein was to treat curatively, including the use of craniospinal irradiation. Our philosophy reflected the belief that after a prolonged interval, the brain repairs some of the original damage caused by the first course of radiotherapy [14–16]. Merchant et al. [14] has recently published a series of recurrent ependymoma showing the feasibility of high dose re-irradiation. Most of the tumors in this series were in the posterior fossa, and thus treated with significant cumulative brainstem doses. Unfortunately, brainstem injury represents a catastrophic toxicity as compared to supratentorial brain injury. The cause of death in our first patient was likely a brainstem injury as reflected by an unreactive pupil and loss of respiratory regulation. The differential diagnosis for the cause of death included tumor progression, cerebral edema, and radiation-induced brainstem injury. Given the short interval from treatment to patient death, the former two appear most likely. The second patient died as persistent tumor or scarring in the ventricles caused an intractable hydrocephalus.

While our experience represents only two isolated cases, it suggests that radiation-induced medulloblastoma is a disease entity that may not respond to aggressive re-irradiation, particularly with disseminated disease. Systemic options including high-dose chemotherapy regimens followed by stem cell rescue could be considered. There have been several reports of high-dose chemotherapy in the treatment of relapsed medulloblastoma [17, 18], and emerging data on the use chemotherapy regimens without radiotherapy in the upfront setting [19, 20]. These generally have included alkylating agents and platinum compounds. The current Children's Oncology Group trial for high risk medulloblastoma uses an induction regimen of vincristine, etoposide, cyclophosphamide, and cisplatin with or without high dose methotrexate. While the role of chemotherapy in adult medulloblastoma is uncertain, several previous pediatric trials have allowed young adults to participate, and this issue likely requires consideration in the radiation-induced variant.

## Conclusion

Radiation-induced medulloblastoma is a rare, but highly aggressive tumor. Surgery followed by full-dose radiotherapy may be considered a possible therapeutic approach. Given prior radiotherapy, however, this cannot always be optimally accomplished. Further reports are necessary in order to fully characterize this disease entity.

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