Child's Nervous System
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CASE REPORT

Radiation-induced spinal cord glioblastoma subsequent to treatment of medulloblastoma: case report

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Abstract

Medulloblastomas are one of the most common malignant pediatric brain tumors. Therapy has evolved into multimodality treatments consisting of surgery, radiation, and adjuvant chemotherapy. While craniospinal radiation remains standard for patients older than 3 years of age, it is not free of side effects and long-term complications. The development of malignant gliomas following therapy is a well-documented phenomenon. However, the majority of these radiation-induced glioblastomas (RIG) are intracranial, and intraspinal lesions are rare. The patient is a 22-year-old female with a history of a posterior fossa medulloblastoma diagnosed 8 years prior for which she underwent surgical resection followed by adjuvant chemotherapy and craniospinal radiation. Surveillance imaging showed no evidence of recurrence or new lesions for the following 5 years. She presented with nausea and vomiting and imaging revealing a new intramedullary cervical spinal cord lesion. She then developed acute quadriplegia several days after presentation. She underwent a cervical laminectomy and resection of this lesion, which was initially diagnosed as recurrent medulloblastoma before genomic analysis ultimately revealed it to be a RIG. Spinal RIGs that occur secondary to treatment for an intracranial neoplasm are exceedingly rare. The majority of spinal cord RIGs have been reported secondary to treatment for tumors outside of the neuroaxis, while the majority of RIGs secondary to treatment for intracranial tumors remain intracranial. Nevertheless, RIGs are associated with a short clinical history, aggressive progression, and poor outcome.

Keywords Oncology · Glioblastoma · Medulloblastoma · Spinal cord · Radiation

Abbreviations

GBM	Glioblastoma
MRI	Magnetic resonance imaging
RIG	Radiation-induced glioblastoma

Introduction

Medulloblastomas are one of the most common malignant brain tumors, representing approximately 9.2% of pediatric brain tumors in children aged 0–14. Treatment is multimodal and includes surgery, radiation, and adjuvant chemotherapy. [1] While craniospinal radiation remains standard, it is not free of side effects, and the development of malignant gliomas following radiation therapy is a well-described rare complication. [2–4] The majority of these radiation-induced glioblastomas (GBM, RIG) are intracranial, and intra-spinal lesions are rare. [5] We present here the unusual case of a 22-year-old patient who presented with a spinal cord GBM secondary to the craniospinal radiation she received for her cerebellar medulloblastoma at the age of 13.

Case report

A 13-year-old healthy female with no past medical history presented with several weeks of headaches and vomiting. Magnetic resonance imaging (MRI) revealed a 4.5-cm contrast-enhancing cystic cerebellar mass that involved the vermis and extended into the fourth ventricle, causing obstructive hydrocephalus (Fig. 1A). She then underwent placement of an external ventricular drain and a suboccipital craniotomy

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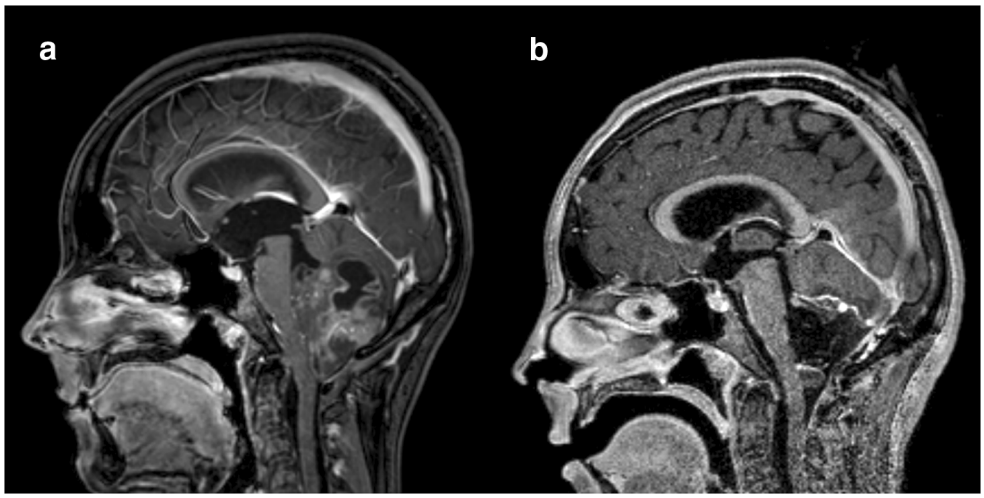

Fig. 1 Preoperative magnetic resonance imaging of the patient's brain revealing a 4.5-cm contrast-enhancing cystic midline cerebellar mass that involved the vermis and extended into the fourth ventricle, resulting in obstructive hydrocephalus (**A**); post-operative imaging revealing gross total resection of the aforementioned mass (**B**)

for resection of the mass. Postoperative MRI showed gross total resection (Fig. 1B). The pathology was medulloblastoma, non-WNT/non-SHH type. It was histologically classic and immunonegative for GAB1, YAP1, β-catenin, and p53 (Fig. 2). MRI of her spine revealed no other lesions. She underwent nine cycles of chemotherapy with lomustine, cisplatin, vincristine, and cyclophosphamide, as well as craniospinal radiation of 23 Gy with a posterior fossa boost of 54 Gy with good results. Surveillance imaging for the following 5 years did not show any recurrence or development of new lesions.

She then presented at the age of 22 with several episodes of nausea and vomiting, although no motor or sensory symptoms. Repeat imaging showed no intracranial recurrence, but did reveal a new enhancing intramedullary lesion within the upper cervical spine (Fig. 3A). Three days later, she developed an acute onset left-sided neck pain and left upper extremity weakness that progressed to her left lower extremity. Repeat MRI showed a slight increase in the size of the spinal cord lesion with decreased enhancement and a new focus of restricted diffusion within the left anterolateral spinal cord (Fig. 3B). After her MRI, the patient had a seizure-like episode with lip smacking and head turning. She became apneic and was intubated. Afterwards, she was able to open her eyes and follow commands with facial movements, but unable to move her extremities. She underwent a cervical laminectomy and biopsy of the lesion, which was grossly necrotic. Neuromonitoring revealed no motor or somatosensory evoked potentials or D-wave monitoring signals throughout the procedure. Final pathology was medulloblastoma, non-WNT/non-SHH, histologically classic (Fig. 4). Similar to her initial tumor, it was immunonegative for GAB1, YAP1, β-catenin, and p53. Fluorescence in situ hybridization showed no evidence of monosomy 6, MYCN, or MYC gene amplification.

Her case was discussed at a multidisciplinary tumor board and surgical resection was recommended. She underwent

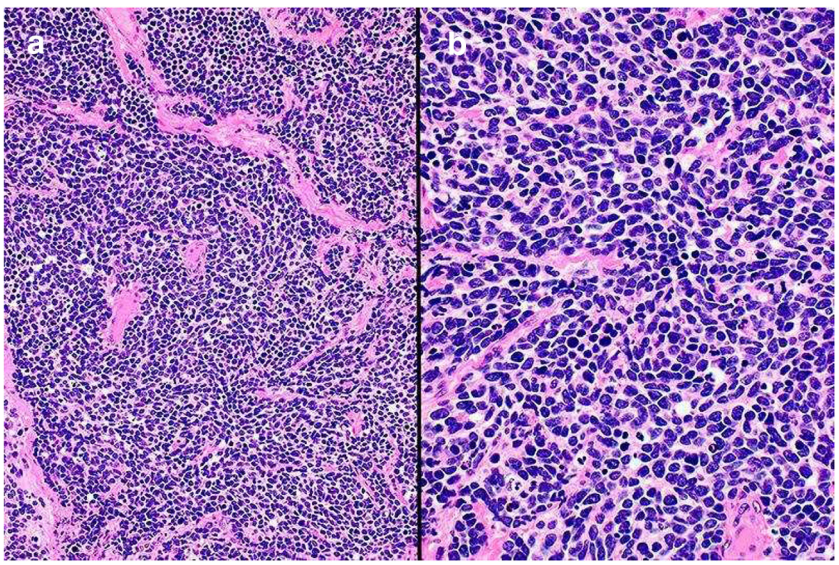

Fig. 2 Low (**A**) and high (**B**) power magnification histopathological images revealing small round undifferentiated blue cells with mild to moderate nuclear pleomorphism characteristic of medulloblastoma. Homer-Wright rosettes can be observed in each image. This specimen was histologically classic and immunonegative for GAB1, YAP1, β-catenin, and p53

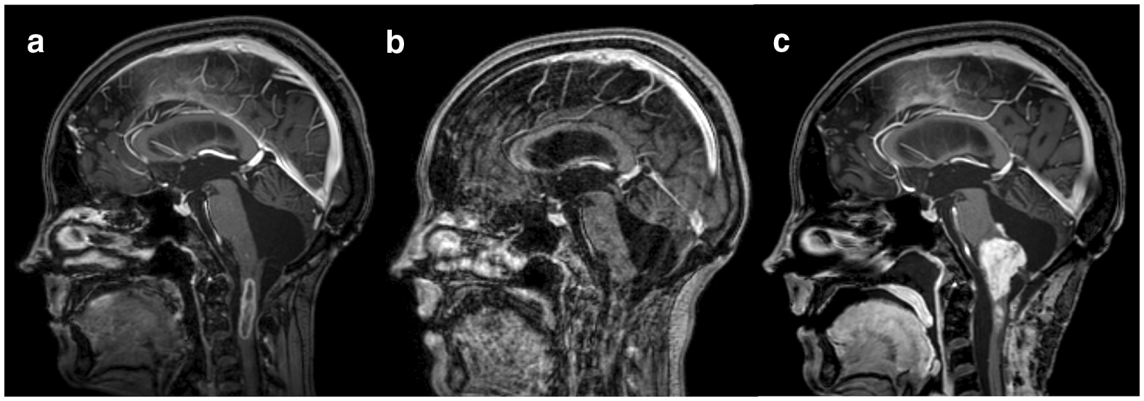

Fig. 3 Magnetic resonance imaging revealing a new enhancing intramedullary lesion within the upper cervical spine from C1 to C3 (**A**). A repeat MRI showed a slight increase in the size of the spinal cord signal abnormality, a decreased amount of enhancement, and a new focus of restricted diffusion within the left anterolateral spinal cord at C2–C3 concerning for a spinal cord infarct (**B**). Subsequent MRI showing progression of her disease with the mass now involving the brainstem as well as multiple new nodular enhancing masses within the cerebellum (**C**)

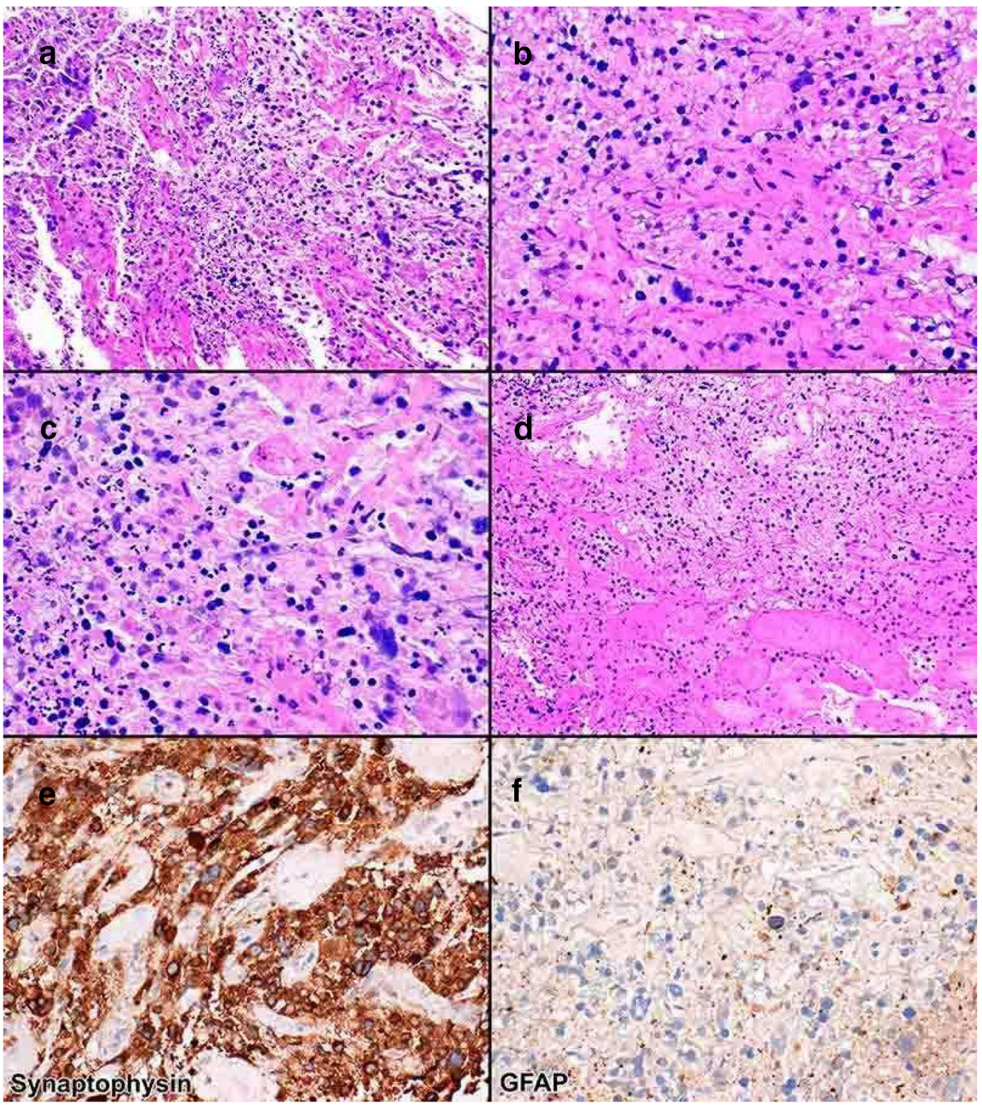

Fig. 4 Low (**A**, **D**), medium (**B**), and high (**C**) power magnification histological imaging from the re-resection of the patient's cervicomedullary tumor revealing hypercellular neoplasm with large areas of necrosis (**D**). The tumor cells appear to have moderate amount of cytoplasm and moderate to marked nuclear pleomorphism. Many multinucleated tumor cells are present. Cells are strongly synaptophysin immunopositive (**E**). Rare cells are immunopositive for GFAP (**F**)

further resection of the lesion and the pathology was only hemorrhage and necrotic tissue. Therefore, the initial biopsy was sent for a second opinion and was determined to be a RIG due to the areas of necrosis, thrombosed vessels, occasional tumor cells positive for YAP1, and amplification of PDGFRA as detected by fluorescence in situ hybridization, which is a possible driver in the development of RIG. [6] Repeat imaging showed progression of her disease with the mass involving the brainstem and multiple new nodular enhancing masses within the cerebellum (Fig. 3C). The family ultimately decided upon comfort care.

Discussion

Medulloblastomas are the most common subset of embryonal central nervous system tumors with a peak incidence during the first decade of life. [1] Treatment includes surgery, radiotherapy, and chemotherapy. Following surgical resection, the craniospinal axis is treated with radiotherapy in patients older than 3 years of age and the posterior fossa receives an additional dosage of irradiation as 50–70% of recurrences occur at this site. [1] Cahan et al. established the following diagnostic criteria for radiation-induced cancers in 1948: (1) a relatively long, asymptomatic latent period must exist between radiation and tumor development, (2) the tumor must arise within the irradiated area, (3) the tumor must be histologically different than the original neoplasm, and (4) the patient must not have any genetic conditions that predispose them to the development of tumors. [4, 7] The exact incidence of all radiation-induced neoplasms is difficult to estimate due to confounding factors such as patient lifestyle and genetic syndromes. The British Childhood Cancer Survivor Study reported a 13% incidence after a median follow-up of 24.3 years and the Childhood Cancer Survivor Study reported a relative risk of 2.7 for a secondary neoplasm following radiotherapy.[8]

The incidence of radiation-induced brain tumors is low at approximately 1%. [9] The incidence of radiation-induced spinal cord tumors is unknown at this time, but primary spinal cord GBMs are rare tumors, accounting for 1–5% of all GBMs and 1.5% of all spinal cord tumors. [10] The development of a spinal cord RIG after treatment of medulloblastoma is rare. The majority of spinal cord RIGs occur after radiation treatment of non-neurologic head and neck tumors or the mediastinal radiation performed for hematologic malignancies. [10–15] The majority of RIG secondary to treatment of medulloblastoma occur at the site of the primary pathology or at other intracranial locations. [9, 16–19] There is one case of a cervical spinal cord anaplastic astrocytoma that occurred 17 years after craniospinal radiation for a cerebellar medulloblastoma. [5] A study evaluating the genomic analysis of recurrent medulloblastoma after radiotherapy found that 5 of 17 patients had secondary GBM, not recurrent medulloblastomas. All five of the secondary GBMs and none of the recurrent medulloblastomas had non-silent mutations in PDGFRA, implicating it as a key driver in RIG development following radiotherapy for medulloblastoma. The RIGs in this study had polymorphic nuclei, long cytoplasmic processes, microvascular proliferation, and necrosis, which were different from the medulloblastomas. [6]

The prognosis of RIGs is poor with an aggressive course and short median survival. Paulino et al. found that median survival after diagnosis of RIG was 11 months with 1-, 2-, and 5-year overall survival rates of 37.1%, 13.0%, and 4.3%. [3] Yamanaka et al. found that grade III and IV radiation-induced gliomas had a median overall survival of 11 and 10 months, respectively. [4] Carret et al. found a median survival of 9.75 months in 18 pediatric patients with secondary grade III and IV intracranial tumors. [20] Unfortunately, treatment options are limited in patients with spinal cord RIGs as surgical debulking is associated with high rates of morbidity and radiation can be risky as these patients have received prior radiation, thereby limiting treatment to chemotherapy. Carret et al. reported that extent of resection and re-irradiation did not improve outcomes and that the patients receiving temozolomide had the longest survival. [20] However, Paulino et al. found that surgery and chemotherapy did not offer survival benefit while re-irradiation did. [3]

Conclusion

Medulloblastomas are a common pediatric brain tumor and its current standard of care consists of multimodality treatment requiring surgical resection followed by craniospinal radiation and adjuvant chemotherapy. This case is unique as it is the first reported case of a spinal cord RIG that occurred after radiation for medulloblastoma. It shows the necessity of long-term follow-up and the need for serial imaging as new pathology can develop in a delayed manner in sites distant to the original pathology. RIGs are a rare entity, particularly in the spinal cord, and prognosis is poor as is consistent with the natural history of GBMs. Optimal treatment has yet to be defined.

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Michael Kim, Jared Cooper, and Ilya Rybkin. The first draft of the manuscript was written by Michael Kim and Ilya Rybkin. All authors commented on previous versions of the manuscript and participated in revisions. All authors read and approved the final manuscript.

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Compliance with ethical standards

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Consent to participate Consent was unable to be obtained as patient unable to be contacted.

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Code availability Not applicable.

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