Development of multifocal glioblastoma after radiotherapy for craniopharyngioma: illustrative case

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BACKGROUND Radiation-induced glioblastoma (GBM) in patients previously treated for craniopharyngioma is a rare phenomenon. To the authors’ knowledge, only seven cases have previously been documented in the literature.

OBSERVATIONS Herein, the authors report a case of a patient presenting with a new diagnosis of multifocal GBM 15 years after having received adjuvant radiotherapy for a craniopharyngioma. Magnetic resonance imaging revealed an extensive enhancing infiltrative lesion in the right frontal lobe as well as two satellite lesions in the contralateral frontal lobe. Histopathology on biopsy was consistent with GBM.

LESSONS Even though this case is rare, it is nevertheless important to recognize GBM as a potential side effect of radiation. Long-term follow-up in postradiation craniopharyngioma patients is crucial for early detection.

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KEYWORDS glioblastoma; radiation therapy; craniopharyngioma

Craniopharyngiomas are histologically benign, locally aggressive, primary intracranial neoplasms treated with resection and adjuvant radiation. Various radiotherapy-associated side effects have been documented; however, the development of glioblastoma (GBM) is exceedingly rare. Herein, we report a case of a 24-year-old female patient with a prior history of craniopharyngioma status postresection and postradiation presenting with multifocal GBM in order to emphasize the need to recognize GBM as a potentially fatal sequela despite its rare incidence in this context.

Illustrative Case

A 24-year-old female presented with generalized weakness, gait impairment, encephalopathy, and new-onset aphasia for the past week. The patient had a prior history of craniopharyngioma at 9 years old and had undergone resection and radiation treatment. She was subsequently followed up with biannual brain magnetic resonance imaging (MRI) without evidence of disease for 15 years until brain MRI (Fig. 1) showed an extensive infiltrative enhancing lesion in the frontal lobes with corpus callosum involvement and two satellite lesions. The initial differential diagnoses included high-grade glioma, metastases, atypical infection, and delayed radiation necrosis. Computed tomography (CT) of the chest, abdomen, and pelvis did not reveal the presence of primary cancer, reducing the likelihood of metastatic disease. Despite leukocytosis (13.2 × 10^3/mm^3, normal range 4.5–10.0 × 10^3/mm^3) during hospitalization, cerebrospinal fluid sampling did not yield evidence of an infectious cause. Because these results did not yield evidence of a metastatic or infectious diagnosis, stereotactic biopsy was conducted for further tissue diagnosis.

Histopathology showed extensive cytological atypia with profound endothelial proliferation and multiple mitotic cells, consistent with the diagnosis of GBM (Fig. 2). Immunohistochemistry analysis demonstrated increased cellular proliferation (Ki-67+) and expression of astrocytic marker (glial fibrillary acidic protein +). Staining with glioma prognostic markers revealed a molecular profile of wild-type isocitrate dehydrogenase 1 (IDH1) and ATRX. Negative expression of neural and endocrine cells (synaptophysin), as well as epithelial cells (pancytokeratin, cytokeratin 5/6), effectively excluded recurrent craniopharyngioma as a potential diagnosis. Given the extent of disease, the lesion was not amenable to resection, and her

ABBREVIATIONS GBM = glioblastoma; IDH1 = isocitrate dehydrogenase 1; MRI = magnetic resonance imaging; RIG = radiation-induced glioblastoma.

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prior history of radiation precluded her from additional radiotherapy. The patient was initiated on palliative temozolomide. Unfortunately, there was persistent progression of disease, and she was ultimately discharged to home hospice. The patient died 5 months after the initial diagnosis of GBM.

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

To the best of our knowledge, this case is the first reported case of a multifocal GBM after radiation therapy for craniopharyngioma. This case of GBM also involved primary and satellite lesions in the frontal lobe, as well as the first description of corpus callosum involvement, whereas prior reported cases have described lesions in the temporal, temporoparietal, frontoparietal, and basal ganglia/brainstem areas. Unfortunately, our patient presented with an IDH wild-type tumor, suggesting a primary GBM. This further suggests a unique mechanism for tumor induction, distinct from the more common secondary gliomas seen in younger populations. Specifically, studies have suggested that up to 59% of females and 44% of all 21- to 40-year-old patients with glioma demonstrate an IDH mutation. Analysis of female patients with GBM has even suggested a relatively common rate of IDH mutation at 36%. The presentation of our 24-year-old patient, with an IDH wild-type tumor status, represented a more unique molecular status and unfortunately portended a worse prognosis than the more commonly reported GBMs in her age group. The unique features of this case emphasize how GBM after radiation therapy can have varying presentations.

The treatment of craniopharyngioma typically includes surgery alone, irradiation alone, or a combination of the two modalities, with the goal of minimizing long-term morbidity and hypothalamic damage. For tumors invading into the hypothalamus or other critical structures, gross-total resection becomes less feasible, and patients are instead treated with external beam radiotherapy alone or with limited surgery, which includes partial resection, cyst fenestration or aspiration, catheter and Ommaya reservoir placement, or cerebrospinal fluid diversion. Multiple radiotherapy options are commonly employed as adjuncts to surgery. Radiation photon-based therapy can be administered in the form of external beam radiation therapy, whereby fractionated radiation allows homogeneous dosing to larger tumors. Alternatively, more focused radiation can be provided via stereotactic radiosurgery in smaller lesions, more effectively limiting radiation doses to adjacent tissues. However, some studies have suggested the potential for more limited tumor control efficacy with stereotactic radiation. Brachytherapy, although less commonly

FIG. 1. A: MRI 1 year prior to diagnosis. B–D: Hyperintense, extensive lesions in the bilateral frontal lobes. The mass crossed the midline and involved the corpus callosum. E: Five months after temozolomide showing progression of the mass and a hemorrhagic cyst. A, C, E: T1-weighted postgadolinium contrast imaging; B: T1-weighted imaging with no gadolinium contrast; D: T2-weighted fluid-attenuated inversion recovery.
employed, does allow direct implantation of radioisotopes within cystic portions of tumor, often administered via an Ommaya reservoir. Another radiation option, proton beam therapy, offers an alternative to photon-based treatments with protons depositing treatment at specific points along the treatment path, limiting irradiation of normal cortex. Although treatments vary in efficacy and side effects, there remains some collateral dose with each radiation modality, necessitating continued improvements in adjuvant therapies for craniopharyngioma. Finally, pharmacological treatment options are more limited, with bleomycin and interferon-alpha administered via an Ommaya catheter. These treatments have more limited efficacy at long-term tumor control, making them adjuncts to the above treatment options.

As such, radiation therapy remains an integral component of multimodal treatment in pediatric neoplasms, including craniopharyngiomas. Postradiotherapy complications have been commonly documented; however, radiation-induced glioblastoma (RIG) is a rare and devastating consequence. Prior studies characterizing the incidence of RIG are scarce, but the risk of secondary glioma after radiation therapy has been estimated to be 1.7% at 10 years and 2.7% at 15 years. In a prior review of radiation-induced malignant glioma in 92 patients with various primary malignancies, 10.9% of these cases had multifocal secondary neoplasms. RIG portends a poor prognosis, with an average survival of 9.7 months after diagnosis and a 2-year survival rate of 7.3%. Although the most common brain tumors associated with RIG are pituitary adenomas and medulloblastomas, seven cases of RIG have been described in patients with craniopharyngioma postradiation. Among the seven cases, the age at which they received radiation ranged from 4 to 22 years old, and the latency period to GBM diagnosis ranged from 6 to 25 years. The mean latency of the eight known cases, including our case, is 11.3 years.

In general, radiation-induced glioma is diagnosed on the basis of the following four criteria: (1) tumor within the previous irradiation field, (2) sufficient latency time between the original and the new tumor, (3) histology of the new tumor is distinct from the original, and (4) presence of a new clinical manifestation. The histopathological examination of the biopsy confirmed GBM with widespread cytologic atypia, endothelial proliferation (asterisk), and mitosis (arrow), features consistent with GBM. The biopsy also revealed increased astrocytic (GFAP) and proliferative (Ki67) signals. Recurrent craniopharyngioma was excluded because the biopsy did not indicate presence of neural and endocrine cells (synaptophysin) or epithelial cells (pancytokeratin and cytokeratin 5/6). Markers commonly associated with poor GBM prognosis were demonstrated by positive wild-type IDH1 and ATRX expressions. Recurrent craniopharyngioma was excluded because the biopsy did not indicate presence of neural and endocrine cells (synaptophysin) or epithelial cells (pancytokeratin and cytokeratin 5/6).
the absence of pathological conditions predisposing to tumor developments. Both increasing intracranial radiation dose and volume have been shown to directly correlate with glioma grade. The average dose of radiation-induced grades II and IV glioma is estimated to be 29.7 ± 18.4 Gy and 37.3 ± 17.5 Gy, respectively. Of note, the total dose for craniopharyngiomas ranges between 50 and 54 Gy.

Lessons

Despite the infrequent occurrence, it is imperative to recognize GBM as a potentially fatal sequela of radiation therapy in patients with craniopharyngioma even decades after exposure. Because RIG is rare and the presentation can overlap with other pathologies, tissue biopsies should be considered for proper diagnosis. Last, long-term follow-up with serial imaging remains critical for early detection and management in this patient population. Although this case gives insight into considerations after radiation therapy for craniopharyngioma, a limitation of the study is that it may have limited generalizability to a larger population of these patients, an inherent limitation of case studies. Further research is needed to characterize GBM status after radiation therapy in patients with craniopharyngioma to improve quality of life and outcome in these patients. In conclusion, this case emphasizes that GBM is a potentially devastating sequela of radiation therapy in patients with craniopharyngioma and that tissue biopsies and long-term follow-up with serial imaging are essential for early detection and recognition of these patients.

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References


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Conception and design: Attenello. Acquisition of data: Lin, Attenello. Analysis and interpretation of data: Yuan, Liu, Attenello. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Yuan. Administrative/technical/material support: Yuan, Min, Liu.

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