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Case Report

Meningioma transformation to glioblastoma following stereotactic radiosurgery: A case report and review of the literature

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ABSTRACT

Background: Meningiomas are the most common primary intracranial tumor with increasing incidence. Stereotactic Radiosurgery Gamma Knife (SRS-GK) is a commonly used modality for neoadjuvant and adjuvant treatment of these tumors and is often necessary for long-term disease control, particularly for the World Health Organization grade II/III meningiomas. While there is strong evidence to support the use of SRS-GK for meningioma, there exists a risk of secondary malignancy that is not well understood. We report a case of glioblastoma (GBM) that arose near the bed of a meningioma previously treated with SRS-GK and discuss other cases of GBM that emerged at a site of meningioma reported in the literature.

Case Description: A 79-year-old female with a history of a blood-clotting disorder presented to the hospital with sudden facial sensory disturbances. On magnetic resonance imaging (MRI), a homogeneously enhancing lesion was observed in the right temporal lobe, consistent with a meningioma. Following 2 years of surveillance, the patient underwent SRS-GK for enlargement of the lesion. The patient later presented with headache and gait instability 12 years following SRS-GK. MRI revealed a large ring-enhancing lesion with surrounding edema histologically confirmed to be a GBM. At 9 months following initial tumor resection and a combination of radiotherapy and temozolomide, the patient was neurologically intact.

Conclusion: There is a very small risk of meningioma to GBM conversion following SRS. Although SRS-GK poses a risk of secondary malignancy, there are some reported cases that underwent malignant transformation without SRS-GK. This suggests that SRS-GK is not the only factor in transformation and is a reasonable therapeutic modality to consider utilizing. Patients and their families should be appropriately counseled on the potential risks of radiation therapy, even for benign lesions like a meningioma.

Keywords: Gamma knife, Glioblastoma multiforme, Malignant complication, Meningioma, Stereotactic radiosurgery

INTRODUCTION

Meningiomas and glioblastoma (GBM) are among the most common primary benign and malignant brain tumors, respectively.[7] Meningiomas are overall the most common intracranial tumors, with an estimated age-adjusted incidence of 8.56/100,000 in the female population, while GBM has an age-adjusted incidence of 3.22/100,000.[2,14] Complete resection

of a meningioma often leads to a cure whereas gross total resection (GTR) of GBM is thought to be unattainable given the infiltrative nature of these lesions and carries a dismal prognosis. Although meningiomas are generally benign, the location and extent of invasion of vital brain structures may limit complete surgical resection, necessitating the use of adjuvant or salvage stereotactic radiosurgery (SRS) for disease control.[9] This becomes exceedingly more important in Grade II and III meningiomas which exhibit higher rates of recurrence.[5] The development of GBM following radiosurgery for benign meningioma is rare but represents a devastating complication as radiation-induced GBM carries a prognosis similar to their *de novo* counterparts.[17] To the best of our knowledge, the case presently reported is the tenth such occurrence of an emergency of GBM in the bed of meningioma, and the fourth such case in settings of SRS Gamma Knife (SRS-GK).

CASE PRESENTATION

A 79-year-old female with a medical history of Factor V Leiden (FVL) and venous thromboembolism (VTE) presented with a sudden bursting sensation above the right eye. Magnetic resonance imaging (MRI) of the brain revealed a homogeneously enhancing 2.0 × 2.1 × 1.9 cm lesion in the right temporal lobe and right sphenoid wing, consistent with a meningioma [Figure 1]. Two years later, on a routine surveillance MRI scan, the lesion enlarged to 2.7 cm in diameter and the patient elected to undergo SRS-GK. The patient underwent treatment with 15 Gy to the 50% isodose line and without complication. Following SRS-GK, the patient remained neurologically intact with stable scans on serial imaging. Twelve years after SRS-GK, she presented with 10 days of headache and gait imbalance. MRI brain with and without gadolinium was obtained depicting a 5.0 × 4.3 × 2.7 cm right frontal ring-enhancing lesion [Figure 2]. The mass extended inferiorly toward the anterior temporal pole with surrounding vasogenic edema and a 7 mm midline shift with right subfalcine herniation.

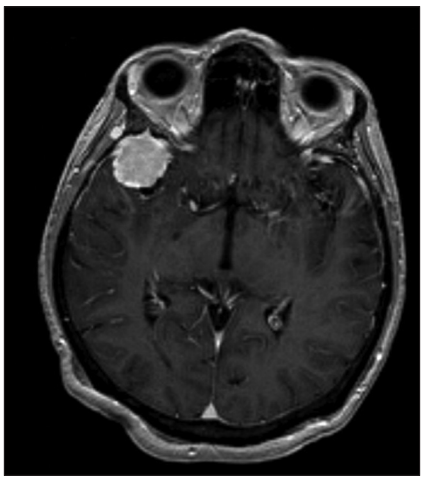

Figure 1: Axial brain magnetic resonance image with gadolinium depicting probable meningioma before gamma knife radiosurgery.

Before elective scheduled surgery, she was placed on a heparin drip given her history of FVL and VTE. Two days following the heparin drip initiation, the patient developed a headache with nausea and emesis. A non-contrast head computed tomography was obtained and showed significant right frontal hemorrhage, increased edema, and worsened midline shift up to 16 mm. She was taken emergently to the operating room for hematoma evacuation. Following careful removal of the hematoma, areas of the lesion were biopsied. Pathologic analysis revealed isocitrate dehydrogenase 1 and 2 wild-type the World Health Organization (WHO) grade IV GBM multiforme with intact retained α thalassemia/mental retardation syndrome X-linked (ATRX), loss of NF1 gene, and combined losses of cyclin-dependent kinase inhibitor A and B. Deoxyribonucleic acid repair gene methylguanine methyltransferase showed promoter methylation [Figure 3].

She underwent adjuvant fractionated radiotherapy with a dose of 34 Gy with concurrent chemotherapy with temozolomide. At the 6-month follow-up, tumor progression was noted, and the patient underwent a repeat right frontal craniotomy for debulking of tumor. At the latest documented follow-up (9 months following initial craniotomy for hemorrhagic GBM; and 3 months following repeat craniotomy), the patient was neurologically intact with a Karnofsky performance score of 100.

Methods

We conducted a comprehensive literature search of electronic online databases (PubMed/MEDLINE) to identify relevant case reports or studies published up to March 2023. A combination of keywords and MeSH terms related to the transformation of meningioma and radiation therapy was used to identify relevant articles. All articles published in the English language were included in the study. Inclusion criteria required the initial lesion to be a meningioma and the secondary lesion to be a GBM originating from a similar or adjacent anatomical location as the primary meningioma. Exclusion criteria included the co-existence of both distinct lesions at the time of initial presentation.

RESULTS

Nine case reports describing the transformation of meningioma to malignant high-grade glioma GBM were identified [Table 1].[6,8,11,12,16,18,21-23] In three cases, SRS-GK was used for treatment of meningioma. Age at the time of the initial lesion diagnosis ranged from 47 to 74 years. One case reported SRS-GK following subtotal resection (STR). One case

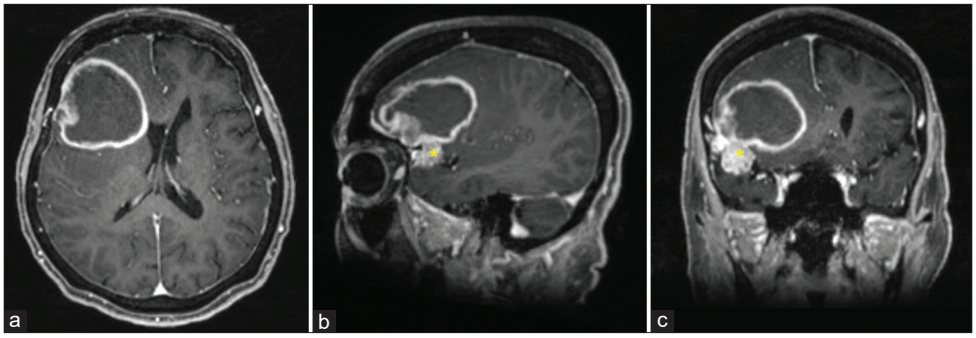

Figure 2: (a) Axial, (b) sagittal, (c) coronal views of brain magnetic resonance imaging with gadolinium 12 years post gamma knife radiosurgery depicting an emergence of a ring-enhancing lesion adjacent to unevenly enhancing meningioma of the Sylvian fissure (asterisks of b and c). The meningioma remained stable or slightly decreased in size.

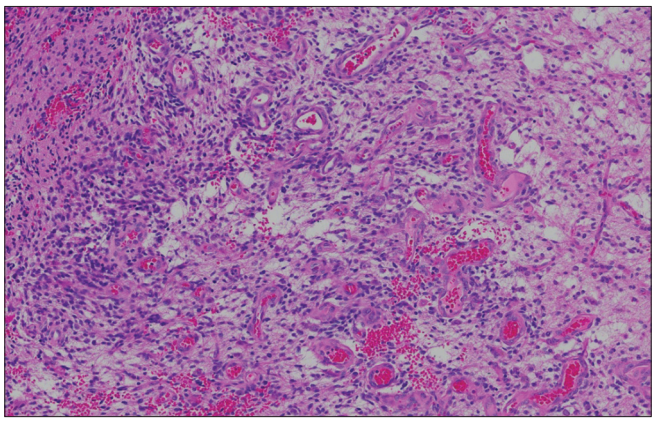

Figure 3: Hematoxylin and eosin-stained sections reveal an infiltrative glioma with endothelial hyperplasia. Original magnification: ×100.

reported three separate treatments with SRS-GK for recurrent tumors following initial GTR. One case reported SRS-GK before STR. The total dosage of radiation delivered ranged from 13 Gy to 20 Gy, with latency periods ranging from 18 months to 7 years. In two cases, the initial meningiomas were classified as WHO Grade I and one case reported a primary WHO Grade II atypical meningioma. All secondary lesions were histopathology-proven high-grade gliomas.

DISCUSSION

SRS is a vital and commonly used tool in the management of both benign and malignant intracranial tumors. Patients with clinical profiles well suited for SRS often stand to benefit from these procedures either as an alternative to more invasive surgery or as a means of continued disease control following surgical resection. Our current patient was initially managed with SRS-GK with a dose of 15 Gy instead of craniotomy for probable meningioma based on MR imaging. The presence of a WHO Grade IV GBM extending from the site of the originally radiated lesion after a 12-year latency period makes this likely an SRS-induced GBM, successfully satisfying the first two criteria employed by Cahan *et al*. to define a radiation-induced secondary malignancy.[1,20] In brief, Cahan *et al*. described a radiation-induced malignancy as being: (1) arising from the site of a previously irradiated field, (2) a latency period of >4 years, (3) tumors must be of different histology, and (4) the radiated tissue must have been normal before radiation treatment.

Radiation-induced glioma is rare and has an incidence rate of ~3% within 15 years of exposure.[17] The evidence on the risk of malignancy following SRS-GK is limited, with few cases reported in the literature. Even rarer is the reported transformation of meningioma to GBM following SRS, as depicted in our present case. Our limited understanding of this phenomenon and the fact that some cases of transformation to GBM identified occurred in the absence of SRS-GK requires us to examine and discuss other factors beyond simply radiation that may contribute to the onset of a secondary malignancy.

Although the co-occurrence of meningioma and GBM is exceedingly rare, the incidence of both tumors is increasing.[10,24] Theoretically, the probability of meningioma and glioma appearing in the same anatomical location is 1 patient every 5 years.[11] Ohba *et al*. reported on the potential of meningeal tumor cells to induce glioma genesis in surrounding glial tissue.[12] Therefore, the possibility of two distinct histological tumors coexisting at initial presentation, although rare, should be considered. Given the extended latency period before the onset of GBM, the radiated tissue may have comprised a mix of meningioma and low-grade glioma (LGG) tumor cells that underwent malignant transformation over time. This is a well-documented occurrence as most LGGs undergo a transformation during their natural disease course and may even have a clinically silent period of up to 14 years (median) as reported by Pallud *et al*.[15] We observed a 12-year latency period in our present case, well within the window of time for transformation previously reported.

Table 1: Transformation of primary meningiomas to secondary glioblastoma ± radiosurgery.

Author	Year	Age	Sex	Primary lesion	WHO Grade	Primary lesion location	Preoperative embolization	Surgery	Extent of resection	Radiation	Timing of radiosurgery	Dose	Latency period	Presentation	Secondary lesion
Labuschagne and Chetty[6]	2019	74	F	Atypical meningioma	II	R parafalcine	No	Yes	STR	SRS-GK	Adjuvant	14 Gy	1.5 years	Seizure	GBM
Lee *et al.*[8]	2012	47	F	Meningotheliomatous meningioma	I	Frontal/olfactory groove	No	Yes	GTR	SRS-GK	Salvage	16 Gy, 13 Gy, 15 Gy (each recurrence)	6 years	Headaches and nausea	GBM
Nazarov *et al.*[11]	2020	69	NR	Meningioma	I	R sphenoid wing	No	Yes	GTR	None	N/A	N/A	3.5 years	Motor and sensory deficits, headaches, nausea	GBM
Ohba *et al.*[12]	2011	72	M	Meningothelial meningioma	I	R frontal convexity	Yes	Yes	GTR	None	N/A	N/A	4 years	Intact (surveillance MRI)	GBM
Pereira *et al.*[16]	2010	70	F	Atypical meningioma	II	R frontal meningioma	No	Yes	GTR	None	N/A	N/A	6 months	Motor deficits	GBM
Sahuc *et al.*[18]	2016	79	M	Fibroblastic meningioma	I	L parietal convexity	No	Yes	GTR	None	N/A	N/A	2 years	Motor deficits and generalized seizure	GBM
Wang *et al.*[21]	2023	66	M	Mixed meningioma	I	L frontoparietal convexity	No	Yes	GTR	None	N/A	N/A	3 years	Intact (surveillance MRI)	GBM
Yaghmour *et al.*[22]	2016	32	M	Meningioma	I	L sphenoid wing	No	Yes	STR	None	N/A	N/A	4 months	Headache and cognitive deficits	GBM
Yu *et al.*[23]	2000	63	F	Fibroblastic meningioma	I	Parasagittal/ occipital lobe	No	No	STR	SRS-GK	Neoadjuvant	20 Gy	7 years	Memory deficits	GBM
Present study	2023	79	F	Meningioma	I	R frontal convexity	No	No	STR	SRS-GK	Neoadjuvant	15 Gy	12 years	Headache and gait imbalance	GBM

SRS-GK, Stereotactic radiosurgery Gamma Knife; GTR, Gross total resection; STR, Subtotal resection; GBM, Glioblastoma; MRI, Magnetic resonance imaging; WHO, World Health Organization; R, Right hemisphere; L, Left hemisphere; M, Male; F, Female; NR, Not reported; N/A, Not applicable; Gy, One gray

Moreover, the previous reports have established the ability of tumors to dedifferentiate into a less differentiated state.[4] Shintaku *et al*. reported the dedifferentiation of meningioma with histopathological analysis showing anaplastic and meningothelial meningioma components juxtaposed.[19] Similarly, Osipov *et al*. reported a case of radiation-induced dedifferentiation of a meningioma into an osteosarcoma.[13] Histopathological analysis showed features of a malignant meningioma adjacent to that of an osteosarcoma. Although a dimorphic appearance on histopathological analysis was not observed in our present case, the potential for tumor cell dedifferentiation and progression to GBM over time remains plausible. Interestingly, next-generation sequencing of GBM in our present case was more compatible with an anaplastic meningioma as opposed to GBM and would be misleading without histologic evaluation. Furthermore, although not applicable to our present case, brain parenchymal damage from surgical resection has been theorized to contribute to malignant cell induction.[3] Coskun *et al.* reported a case of trauma-induced GBM in a 65-year-old patient following a depressed skull fracture.[3] However, this theory lacks robust supporting evidence.

Overall, our findings suggest that there is a very small potential for meningioma transformation to a GBM following initial treatment. Although SRS-GK poses a risk of secondary malignancy, we report several cases of initial lesions that underwent malignant transformation without SRS-GK and as such should not be a significant reason not to utilize this therapeutic modality.

CONCLUSION

The increased use of SRS-GK in the management of benign tumors may mean that neurosurgeons will encounter more radiation-induced secondary lesions requiring further surgical and medical intervention. In clinical scenarios where SRS-GK is employed as an alternative to surgical resection, longer-term surveillance beyond a 5-year mark could be considered. This becomes particularly important in the absence of a tissue-based diagnosis following resection that can rule out the co-existence of more aggressive or cancerous cells. Long-term follow-up and appropriate patient counseling are imperative following initial tumor resection and/or radiation therapy, even in initially benign lesions such as meningioma.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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