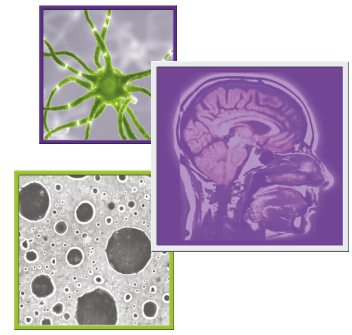
Case Report

CNS Oncology



Next-generation sequencing reveals novel mutations in a collision tumor of glioblastoma and meningioma

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Practice points

- We report novel missense mutations in *TAF1L* (c.410G>A, p.A1056V) and *CSMD3* (c.601T>C, p.H3047R) in the glioblastoma component of a collision tumor consisting of glioblastoma and meningioma.
- Primary intracranial collision tumors are rare, with the most common consisting of glioma and meningioma.
- Imaging alone is not sufficient to identify all intracranial collision tumors, but MRI is the most sensitive modality.
- Intracranial collision tumors should be considered in the differential in cases of suspected meningioma with greater peritumoral edema than expected on imaging.
- Although many believe that intracranial collision tumors arise by chance alone, some evidence exists to suggest that the microenvironment of one tumor could stimulate the development and growth of another.
- *CSMD3* gene expression has been linked to better prognosis in gliomas, but the method by which this occurs has not been elucidated.
- Further investigation is necessary to determine whether the novel mutations in *TAF1L* and *CSMD3* identified in this study are seen in other gliomas existing in collision with other primary intracranial neoplasms, and whether they portend differential survival or potential therapeutic targets for patients with such lesions.
- Next-generation sequencing can be used to differentially examine separate components of a collision tumor, but is limited by the extent to which the components of the collision tumor can be physically separated from one another.

Primary intracranial collision tumors are rare in patients without predisposing factors. We report such a case in a 42-year-old female who presented with headaches and altered mental status. Imaging revealed a single heterogeneous, rim-enhancing lesion in the left parieto-occipital periventricular region, involving the corpus callosum. Stereotactic biopsy demonstrated glioblastoma. Subsequent tumor resection showed histologic evidence of glioblastoma and meningioma. Next-generation sequencing was performed on both tumor components. The glioblastoma exhibited a *CDKN2A* homozygous deletion and novel missense mutations in *TAF1L* and *CSMD3*, while no definitive genetic alterations were identified in the meningioma. Next-generation sequencing may yield insight into molecular drivers of intracranial collision tumors and aid in identifying future therapeutic targets.

Tweetable abstract: Next-generation sequencing (NGS) reveals novel mutations in a collision tumor of GBM and meningioma. NGS has the potential to yield insight into molecular drivers of intracranial tumors and identify therapeutic targets.

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A collision tumor is the occurrence of two histologically distinct neoplasms at adjacent sites. Intracranial collision tumors often arise in patients with a history of radiotherapy or familial neurocutaneous syndromes [1,2]. Outside of such cases, intracranial collision tumors are rare, with the most common type consisting of a glioma and

Future Medicine

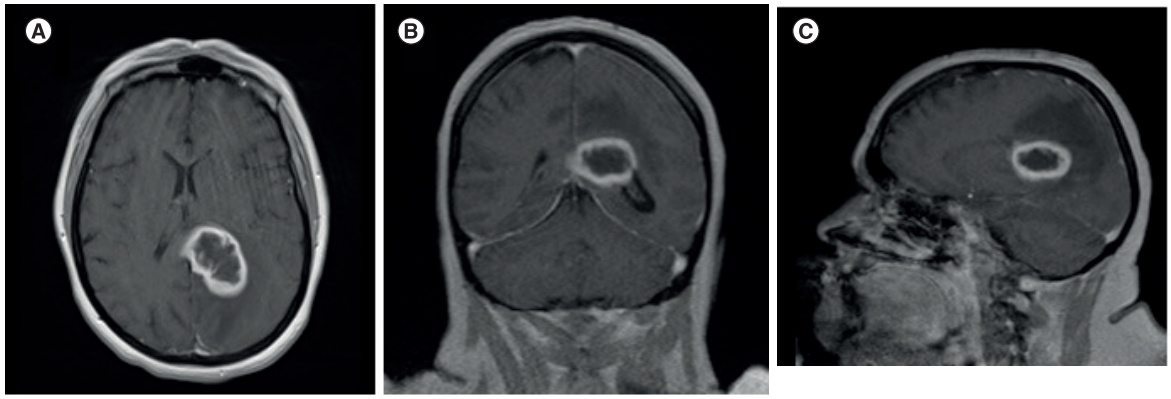

Figure 1. Preoperative cranial T1-weighted magnetic resonance images with contrast. (A) axial, **(B)** coronal and **(C)** sagittal images.

a meningioma [3]. The pathogenesis of collision tumors is still unknown. Some researchers propose common oncogenic drivers [3,4], while others suggest that the microenvironment of one tumor affects the growth of the other [3,5–14] or that these tumors happen asynchronously and randomly [2,15–19]. Approximately 1% of glioblastoma cases occur in close proximity to or collide with a meningioma [3]. We present a case of an intracranial tumor that appeared as one lesion radiographically but demonstrated two histologically distinct tumors. To our knowledge, we are the first to report next-generation sequencing (NGS) results of an intracranial collision tumor of glioblastoma and meningioma.

Clinical summary

A 42-year-old female with a history of seizures, bipolar disorder, thyroid cancer and cervical cancer presented with a month of worsening headaches and memory loss. She had no history of prior head trauma, neurologic surgery or radiation therapy. Neurologic examination revealed no focal neurologic deficit. Brain MRI demonstrated an irregular, heterogeneous rim-enhancing lesion in the left parieto-occipital periventricular region. No other enhancing lesions were identified (Figure 1). The imaging characteristics favored a primary high-grade glioma, but metastasis was also on the differential given the patient's history of malignancy. Systemic CT imaging did not demonstrate evidence of metastatic disease. The patient underwent stereotactic biopsy of the lesion. Pathologic examination of the biopsy revealed glioblastoma, *IDH* wild-type (WHO grade IV). Soon after, she underwent craniotomy for resection of the tumor. Pathology from the resection demonstrated two distinct neoplasms: a glioblastoma (WHO grade IV) and a meningioma (WHO grade I). The patient's postoperative course was complicated by respiratory failure and she died on postoperative day 18 after her family transitioned her to comfort care measures.

Pathologic findings

Histopathology

Microscopic examination of the initial biopsy (Figure 2) demonstrated features of glioblastoma, including nuclear atypia, multinucleated cells, scattered foci of microvascular proliferation and numerous mitoses (seven mitotic figures per ten high-power fields). The biopsy did not show any necrosis, spindle cells or psammoma bodies. Immunohistochemical testing showed diffuse positivity for GFAP, with retained expression of ATRX, rare p53-positive cells and no expression of IDH1, R132H or H3 K27M mutant proteins.

The tumor resection specimen (Figure 3) demonstrated an infiltrating high-grade glioma with extensive necrosis, consistent with glioblastoma (WHO grade IV). Also identified were two fragments of fibrous tissue containing bland spindle cells and numerous psammoma bodies, morphologically consistent with a meningioma (WHO grade I). The fragments of meningioma were surrounded and infiltrated by the glioblastoma. Immunohistochemical testing was performed on tissue containing both meningioma and glioblastoma. GFAP showed diffuse positivity in the areas of tumor histologically consistent with glioma, but was negative in the regions of meningioma. Epithelial membrane antigen and progesterone receptor immunohistochemistry gave positive results in the spindle cells but not within the glioma.

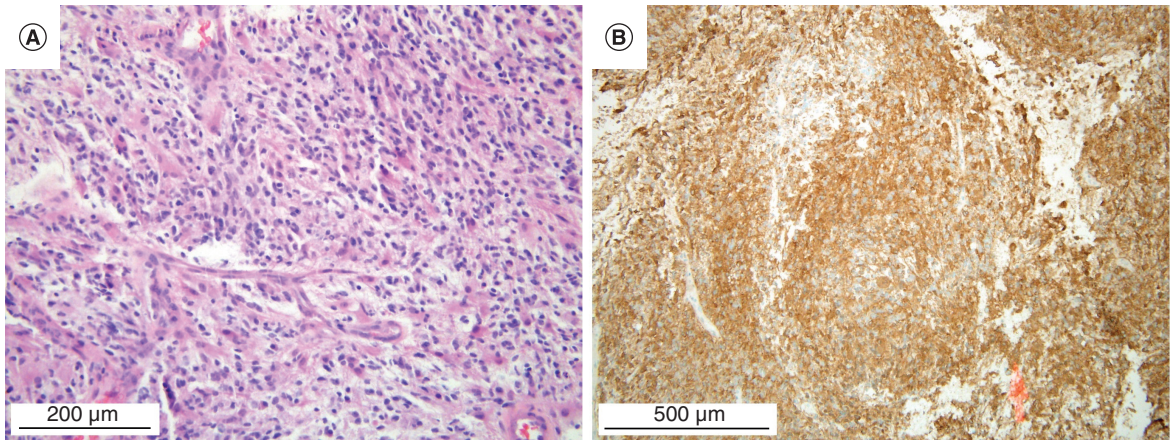

Figure 2. Initial diagnostic biopsy. (A) The lesion demonstrates nuclear atypia, multinucleation and microvascular proliferation. **(B)** The lesion is strongly and diffusely positive for GFAP, confirming a glial neoplasm.

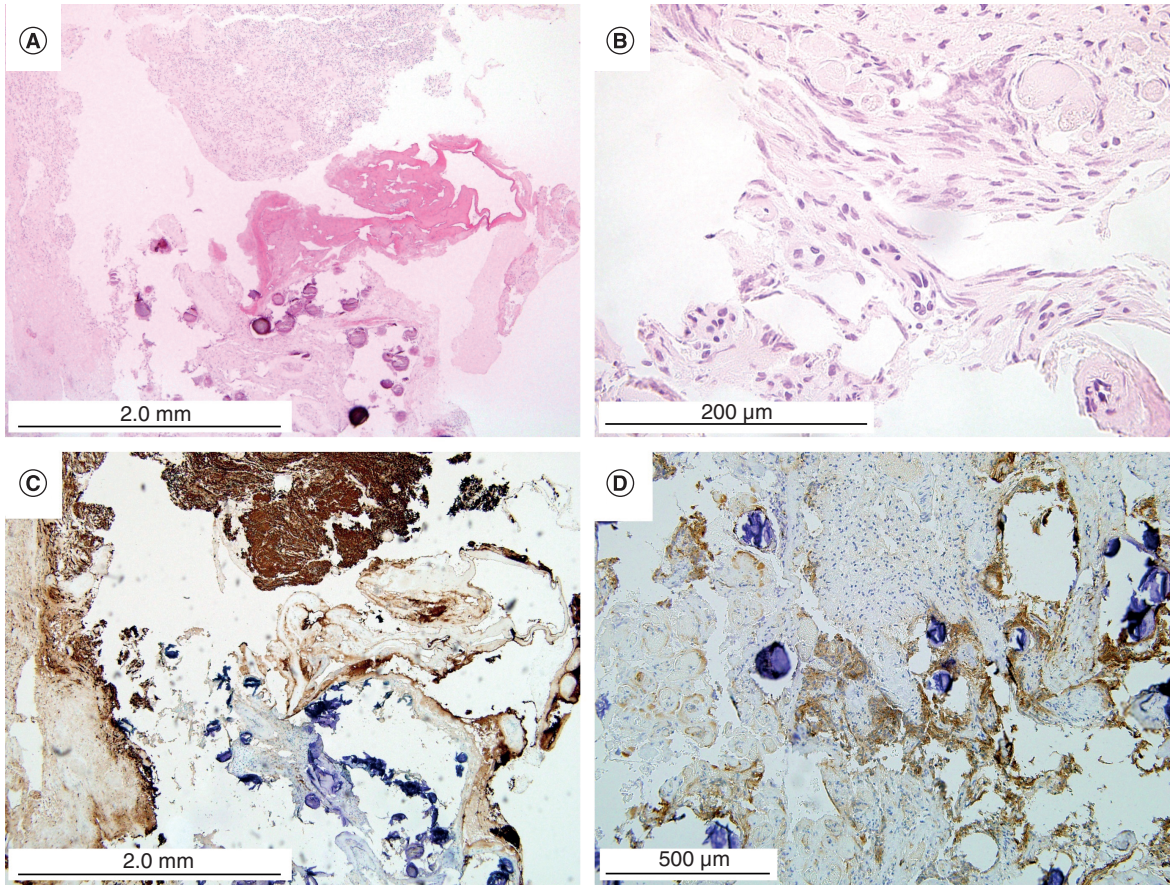

Figure 3. Resection specimen. (A) The lesion contains neoplastic tissue that is histologically identical to the biopsy specimen (top, left), as well as a region of fibrous tissue with psammoma bodies (bottom). **(B)** The fibrous tissue contains cytologically bland-appearing spindle cells. **(C)** GFAP is positive in the regions histologically consistent with glioma and negative in the spindle cell population. **(D)** Epithelial membrane antigen is positive in the spindle cells and negative in the glioma.

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Genetic sequencing results

The assays for *IDH1* and *IDH2* mutations, *TERT* promoter mutations and *MGMT* promoter methylation were negative in the glioblastoma component. No loss of whole chromosome arms 1p or 19q was detected.

NGS, microsatellite instability status, tumor mutation burden and *PD-L1* RNA expression were performed twice on the collision tumor: once with tissue enriched for the glioblastoma component and once with tissue enriched for the meningioma. These assays were performed using the StrataNGS assay (Strata Oncology, MI, USA) via an Ion Torrent-based sequencing platform (ThermoFisher Scientific, MA, USA).

NGS performed on the glioblastoma component (molecularly informed tumor content of 80%) revealed a deep deletion of *CDKN2A* with an estimated copy number of 0 (95% CI: 0.3–0.5), as well as a *TAF1L* c.410G>A, p.A1056V missense mutation at 30% variant allele frequency (VAF) and a *CSMD3* c.601T>C, p.H3047R missense mutation at 14% VAF. The lesion did not demonstrate detectable alterations in any of the other genes frequently mutated in glioblastomas and included in the NGS assay. Additionally, the glioblastoma was determined to be microsatellite stable with a low tumor mutation burden (two mutations per megabase, 95% CI: 0–6) and low *PD-L1* RNA expression (RNA expression score of 2).

The NGS assay performed on the meningioma component revealed the same *TAF1L* A1056V missense mutation seen in the glioblastoma component, but at 15% VAF. No other genetic alterations were detected. Also of note was a lack of mutations or amplifications in *EGFR* or *PDGFRA*. The meningioma was additionally found to be microsatellite stable with a low tumor mutation burden (one mutation per megabase, 95% CI: 0–5). Of note, despite careful microdissection the molecularly informed tumor content was 20%. Thus the assay was unable to determine the presence of deep deletions.

Discussion

This case is unique as it represents a collision tumor of glioblastoma and meningioma which presented radiographically as one lesion on MRI. In addition, the two separate tumor components were not identified intraoperatively or on gross pathologic examination.

Numerous case reports have been published describing intracranial collision tumors. Of these, only 26 cases describe lesions consisting of glioma and meningioma in which the tumors were anatomically adjacent and developed in patients without histories of neurocutaneous disorders or intracranial radiation. See Table 1 for a summary of relevant clinical and pathologic data from these cases.

Eleven cases presented as two distinct, adjacent lesions on preoperative imaging [1,3–5,10,12,13,16,19–21]. Importantly, three of these cases had preoperative CT and MRI performed in which separate lesions were identified by MRI but were thought to represent a single lesion by CT [1,5,12]. There were seven cases in which preoperative imaging showed a single lesion, but an MRI was not performed [2,8,15,16,22,23]. In those cases, two separate components could frequently be distinguished intraoperatively.

Six cases [6,9,11,14,17,21] initially presented as a single lesion on both preoperative imaging and pathologic examination (meningioma in five cases and glioma in one case). Postoperative imaging confirmed the presence of a second lesion within the operative bed between 6 months and 7 years after the first resection. In three of these cases the histologic presence of adjacent or admixed glioma and meningioma was confirmed on subsequent resection [6,9,14].

We identified only two cases which describe a single lesion seen on preoperative MRI. One case describes separate solid and cystic components within the lesion [24]. The other case, published by Ruiz *et al.*, describes an identical scenario to ours in which preoperative MRI suggested a glioma and the meningioma component was only identified histologically [12].

The clinical data described above outline several key points in collision tumorigenesis and preoperative identification of collision tumors. While MRI appears to be much more sensitive than CT in identifying lesions as collision tumors, it is not 100% sensitive – especially in cases demonstrating a meningioma surrounded by edema. Thus the possibility of a collision tumor should be considered during histologic examination of a radiographically singular lesion, and should be carefully ruled out in meningiomas for which the amount of surrounding edema seen on imaging is greater than expected. Additionally, the collision tumor components need not present simultaneously. In a subset of cases, the second tumor component arose within the operative bed of the first component. These cases would seem to corroborate the hypothesis that the microenvironment of one tumor, the consequences of intracranial surgery or a combination of the two may stimulate the development and growth of the second component.

Table 1. Summary of previously described collision tumors consisting of glioma and meningioma.

Author	Year	Age/sex	Meningioma type	Glioma type	Imaging	Synchronous	Two distinct lesions identified simultaneously by imaging?	Ref.
Chen *et al.*	2010	63 F	Fibroblastic meningioma	Glioblastoma	CT, MRI	Yes	CT: no; MRI: yes	[1]
Davis *et al.*	1995	50 M	Meningioma	Well-differentiated astrocytoma (grade 1/3)	CT, MRI	No	N/A	[21]
		67 F	Meningioma	Anaplastic astrocytoma (grade 2/3)	CT	Yes	Yes	
Drlicek *et al.*	2004	51 M	Meningioma, WHO grade I	Glioblastoma, WHO grade IV	CT	Yes	No	[22]
Goyal *et al.*	2003	72 M	Fibroblastic meningioma	Glioblastoma	CT	Yes	No	[15]
Khalatbari *et al.*	2011	12 M	Meningioma	Anaplastic astrocytoma, WHO grade III	CT, MRI	Yes	CT: no; MRI: yes	[5]
Maiuri *et al.*	2005	65 M	Meningioma	Diffuse astrocytoma, WHO grade II	CT	Yes	No	[16]
		66 M	Meningioma	Glioblastoma	MRI	Yes	Yes	
Matyja *et al.*	1995	46 M	Endothelial meningioma	Malignant astrocytoma	CT	Uncertain	No	[8]
		62 F	Endothelial meningioma	Anaplastic astrocytoma	CT	Uncertain	No	
Mitsos *et al.*	2009	73 F	Fibrillary meningioma, WHO grade I	Glioblastoma multiforme, WHO grade IV	MRI	No	N/A	[9]
Nagashima *et al.*	1963	42 M	Fibroblastic meningioma	Fibrillary astrocytoma	Arteriogram	Yes	Yes	[10]
Nestler *et al.*	2007	49 M	Fibrous meningioma, WHO grade I	Glioblastoma, WHO grade IV	MRI	Yes	Yes	[20]
Ohba *et al.*	2011	72 M	Meningothelial meningioma	Glioblastoma	MRI	No	N/A	[17]
Pereira *et al.*	2010	70 F	Atypical meningioma, WHO grade II	Glioblastoma, WHO grade IV	CT, MRI	No	N/A	[11]
Prayson *et al.*	2002	87 F	Syncytial meningioma, WHO grade I	Malignant astrocytoma, WHO grade III	MRI	Yes	No	[24]
Ruiz *et al.*	2015	86 M	Secretory meningioma, WHO grade I	Glioblastoma, WHO grade IV	CT, MRI	Yes	CT: no; MRI: yes	[12]
		22 F	Secretory meningioma, WHO grade I	Anaplastic astrocytoma, WHO grade III	MRI	Yes	No	
Strong *et al.*	1976	56 F	Meningioma	Glioblastoma multiforme	X-ray, isotope scan, angiogram, CT	Uncertain	No	[2]
Suzuki *et al.*	2010	75 F	Meningothelial meningioma	Glioblastoma	MRI	Yes	Yes	[4]
Truong *et al.*	2019	61 F	Fibroblastic meningioma	Astrocytoma, grade II	MRI	Yes	Yes	[19]
Tugcu *et al.*	2006	42 M	Transitional meningioma	Glioblastoma multiforme	MRI	Yes	Yes	[13]
Vaquero *et al.*	1990	75 F	Psammomatous meningioma	Glioblastoma multiforme	CT	Yes	No	[23]
Yaghmour *et al.*	2016	32 M	Meningioma	Glioblastoma	CT, MRI	No	N/A	[14]
Zhang *et al.*	2015	39 M	Malignant meningioma, WHO grade II	Astrocytoma, WHO grade II	CT, MRI	No	N/A	[6]
Zhang *et al.*	2018	66 F	Meningioma, WHO grade I	Glioblastoma, WHO grade IV	MRI	Yes	Yes	[3]

F: Female; M: Male.

To our knowledge, we present the first case of a collision tumor to undergo genomic profiling of each separate component by NGS. In addition to a *CDKN2A* deep deletion, the NGS assay revealed two novel mutations in the glioblastoma component that have not been described previously in gliomas: *TAF1L* A1056V and *CSMD3* H3047R.

TAF1L

TAF1 plays a central role in gene transcription and cell proliferation, and decreased *TAF1* expression is associated with a concomitant reduction in p27Kip1 expression and reduced apoptosis [25]. TAF1-like (TAF1L) is a TAF1 homologue with histone acetyltransferase activity and plays a role in autophagy-dependent apoptosis [26].

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TAF1L gene alterations have been implicated in tumorigenesis or prognosis in a subset of neoplasms of different tissue types, including oral and esophageal squamous cell carcinoma [26–29], pulmonary carcinoid tumors [30], gastric and colorectal cancers [31], melanoma [32] and urothelial cancer [33].

The Catalogue of Somatic Mutations in Cancer and cBioPortal databases identify *TAF1L* mutations, amplifications and deletions in 1.9% of genetically profiled diffuse gliomas, including glioblastoma [34–36]. However, this gene's potential role in the development, progression and treatment of gliomas has not been studied to date.

The *TAF1L* A1056V mutation was present at a lower VAF in the meningioma component compared with the glioblastoma component (15% vs 30%). The meningioma-enriched tissue submitted for NGS was determined to contain only 20% meningioma cells, and the glioblastoma was seen histologically to invade the meningioma component. Additionally, glioblastomas and meningiomas arise from different cell precursors and there is no evidence to suggest a germline *TAF1L* mutation. Taken together, these data would suggest that the presence of the *TAF1L* mutation in the meningioma is due to contamination by the glioblastoma. A thorough literature review did not uncover any published data showing the presence of *TAF1L* mutations in meningiomas.

CSMD3

CSMD3 is a recently discovered member of the *CSMD* gene family [37,38] and is believed to act as a transmembrane receptor that regulates dendritic development [37,39].

Several studies support the role of *CSMD3* as a tumor suppressor in tissues outside the CNS. Frequent *CSMD3* mutations have been identified in non-small-cell lung carcinomas [40,41]. Germline *CSMD3* mutations have been identified in several cases of familial colorectal cancer [42] and *CSMD3* alterations leading to loss of function may be a negative prognostic indicator in sporadic colorectal cancer [43].

The cBioPortal database identifies a variety of *CSMD3* alterations, cumulatively present in 4% of profiled gliomas [34,35]. One study has linked *CSMD3* gene expression to better prognosis in gliomas [44].

CDKN2A

The *CDKN2A* gene is a tumor suppressor that encodes two proteins, p16INK4a and p14ARF, and plays a vital role in the regulation of the cell cycle via the p53 and retinoblastoma signaling pathways [45]. *CDKN2A* deletions are one of the most common genetic alterations in glioblastoma and are associated with a poor prognosis in diffuse gliomas in general [46,47].

Limitations

The limit of detection for predefined genetic alterations in the StrataNGS assay is 5% VAF, while the limit of detection for *de novo* nonsense mutations/frameshift indels is 15% VAF; thus the neoplasms could possess additional clinically significant alterations in genes not assessed by the assay. Given the difficulty in dissecting the meningioma component from the glioblastoma component and the presence of psammoma bodies, the low tumor cellularity of the tissue submitted for evaluation of the meningioma may have also compromised the ability to detect meaningful genomic alterations in that component.

Conclusion

We present a case of an intracranial collision tumor of glioblastoma and meningioma. This case is unique as the separate components of the collision tumor were indistinguishable both radiographically and intraoperatively. To our knowledge, we are the first to report NGS analysis of such a collision tumor. The NGS findings in this case study do not provide a potential for targeted therapy at this time. In the absence of targeted therapies, patients with a collision tumor of glioblastoma and meningioma would undergo chemoradiotherapy postoperatively, with radiation also being delivered to any residual components of the meningioma. However, given the known biology of the genes that were altered in this lesion, there is a possibility that future research will allow for development of targeted therapies. Future NGS data from a larger pool of collision tumors may add to our knowledge of tumorigenesis and reveal potential therapeutic targets, with the ultimate goal of improving patient outcomes.

Future perspective

NGS is a powerful tool for quickly and accurately identifying molecular alterations in a variety of neoplasms. Implementation of NGS in the management of oncology patients can be expected to grow as additional therapeutic targets are discovered. Additionally, NGS will likely be a significant driver in the discovery of such therapeutic

targets as increasingly larger pools of tumors are tested by this modality. It remains to be seen whether the particular molecular alterations outlined in our study will contribute to management of gliomas or primary intracranial collision tumors in which glioma is a component.

Author contributions

All authors made substantial contributions to the conception, design, data analysis and data interpretation of the work; contributed to drafting and revising the manuscript; gave final approval for publication; and agree to be accountable for all aspects of the work.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have attained appropriate institutional review board approval for this research. The work was deemed exempt from institutional review board review and no informed consent was obtained as all study subjects were deceased at the time of study investigation.

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