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GLIOBLASTOMA SECONDARY TO MENINGIOMA: A CASE REPORT AND LITERATURE REVIEW

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Keywords:
Glioblastoma;
Meningioma
Tumorigenesis

ABBREVIATIONS:
CT: computed tomography
EGFR: epidermal growth factor receptor
EMA: epithelial membrane antigen
FLAIR: fluid-attenuated inversion recovery
GFAP: glial fibrillary acidic protein
MRI: magnetic resonance imaging
IDH: isocitrate dehydrogenase
PDGFR: platelet-derived growth factor receptor
RTK: receptor tyrosine kinase
VEGF: vascular endothelial growth factor
WHO: World Health Organization
VHL: Von Hippel-Lindau disease
**ABSTRACT:**

**Background:** The pathophysiologicals underlying meningioma and glioma are quite distinct. The coexistence of those two lesions in a same patient is rare, and that at the same location is even more exceptional.

**Case Description:** We report a case of a 79-year-old man initially presenting a meningioma that was treated by complete excision of the lesion. The patient had two relapses at the same site in which glioblastoma was confirmed histopathologically.

**Conclusions:** Glial transformation meningiomas remains a contentious issue, with coincidental occurrence being the most prevalent explanation. Nevertheless, impairment of the same molecular signaling pathways in both tumor types suggests a common origin. Another hypothesis is that perilesional parenchymal damage from radiotherapy or surgery may lead to glial transformation in the tissues surrounding the original meningioma lesion. Further research is needed to determine if the original tumor or surgery has an oncogenic effect on the adjacent tissue.
CONFLICT OF INTEREST:

None
Glioblastoma secondary to a meningioma: a case report and literature review
P. Sahuc, C. Joubert, A-T Nguyen, A. Faivre, P. Alla, A. Dagain

INTRODUCTION:
Meningioma and glioblastoma have distinctive pathophysiology. Their coexistence in the same patient is rare (less than 60 cases have been described), and their coexistence at the same site is even more exceptional. In fact, there are only a few controversial cases reported in the literature regarding the glial transformation of meningiomas. Some researchers believe that the coexistence and colocalization of these two types of lesions could be the result of parenchymal injury with secondary glial transformation caused by radiotherapy or surgery, whereas others believe that this is coincidental. Indeed, there are only a few published cases that describe the two histological lesions as occurring at the same location without an inducing factor. Here, we present a case of a fibroblastic grade-1 meningioma in the cranial vault with a secondary glioblastoma occurring at the same site.

OBSERVATION:
A 79-year-old man without any relevant medical history presented with left-sided hemicranial bone growth related to a left parietal meningioma infiltrating the adjacent bone. Cranial computed tomography (CT) revealed a dural-based tumor-like lesion contiguous with the meninges in the left parietal lobe with moderate peripheral edema and intralesional calcification. After contrast-agent administration, we observed cranial vault destruction adjacent to the lesion (Figure 1a). Because the bony growth increased in size and the occurrence of right hemiparesis, the patient underwent surgical resection 3 months after initial presentation. The surgery was completed without complications. A postoperative cranial CT scan showed no residual tumor or hemorrhagic lesions. Histological analysis of the resected tissue confirmed a fibroblastic grade-1 meningioma with an epithelial marker antigen (EMA) level of >75% and a Ki-67 index of 3% (Figure 1b). The patient recovered completely from his symptoms. Clinical and radiological follow-up during the following months was uneventful. Two years after surgery, the patient reported back because of the recurrence of right-sided hemiparesis and partial seizures. A cranial magnetic resonance imaging (MRI) examination showed a relapse of the malignant lesion at the same site (Figure 1c) and a second surgical resection was performed. Surgical data showed horizontal invasion of the pia mater and cortical infiltration limited to the gray matter. In addition, the posterior margin of the tumor...
was easily separable from the adjacent parenchyma. Histopathological analysis revealed atypical fibroblastic World Health Organization (WHO) grade-2 meningioma with a high level of glial fibrillary acidic protein (GFAP) expression and a Ki-67 index of 25% (Figure 1d). This unusual early relapse occurred despite favorable immunohistochemical features (low Ki-67 index) of the primary lesion, which led us to look for a syndrome of hereditary cancer predisposition. We found no sign of cutaneous lesion and whole-body CT scan did not disclose associated lesions. Moreover, there was no history of cancer in his family. In the following days, the patient experienced the progressive amelioration of his symptoms, but continued to experience partial seizures. After a multidisciplinary consultation, brain radiotherapy was administered at the surgical site (60 Gy). Six months after radiotherapy, the patient experienced worsening of right hemiparesis, disorientation, and cognitive disorders. A new MRI showed a recurrence of an infiltrating tumor in the left parietal lobe with edema (Figure 1e). Thallium scintigraphy showed high tracer accumulation at the injury sites, suggesting high-grade tumor. The patient underwent a third neurosurgery, during which we observed an extra-axial necrotic lesion invading the cortical grooves. Results of histopathological analysis revealed an atypical fibroblastic WHO grade-2 meningioma (Figure 1f). Nevertheless, after reviewing the three tissue samples in the reference center, the sample from primary lesion corresponded well to a fibroblastic WHO grade-1 meningioma, whereas the samples from the two recurrences were characteristic of a WHO grade-4 glioblastoma. We initiated monthly chemotherapy cycles with temozolomide, which initially led to a one-third decrease in lesion size. Unfortunately, the patient relapsed and died 8 months later.

**DISCUSSION:**

Here we present a case of a patient with meningioma who relapsed with glioblastoma. First, it is important to confirm an accurate initial diagnosis. Except cases of subcortical meningiomatosis, it is generally easy to radiologically and surgically distinguish an intra-axial meningioma with an extra-axial growth from an entirely intra-axial glioma. In the reported case, radiological, surgical, fresh-mount, and histological data were highly suggestive of meningioma. Our review of biopsy samples from two reference centers added weight to the final diagnosis. Clinical and laboratory tests ruled out the possibility that the patient was genetically susceptible to present the two types of lesions, which are possible in systemic diseases, such as phakomatosis, neurofibromatosis, tuberous sclerosis, or Von Hippel-Lindau Disease (VHL).
Even though it is rare, the existence of glioma or meningioma in these genetic disorders have been reported. VHL brain lesions are commonly hemangioblastomas. Cases of glioma have been described, but they are most often characterized as low-grade astrocytomas. VHL meningiomas are even rarer, but germ-line mutation have been reported. Tuberous sclerosis is characterized by the formation of hamartomas in various parts of the body, including the brain. With this disease, brain lesions are typically cortical tubers, subependymal nodules, and subependymal giant-cell astrocytomas. However, there are a few case reports that show the occurrence of high-grade glioma or meningioma in patients suffering from this disorder. Moreover, the two tumor types are part of the diagnostic criteria of neurofibromatosis 2 (NF2). They are rarer in NF1 optic pathway gliomas, with brainstem gliomas being the predominant intracranial neoplasms in this condition. Reports seldom describe low-grade glioma and meningioma.

In our case, there were no further tumors to obtain histological samples for further analysis. Nevertheless, the entire lesion was analyzed after the first and the second surgeries. Histopathological examinations showed no genetic mutations, including p53 mutations. An eventual gliosarcoma was eliminated after the samples were reviewed in the reference center by an operator affiliated to POLA’s network. Moreover, since our patient did not undergo radiotherapy before the second surgery, radiotherapy-induced glioma was excluded from the diagnosis.

From our point of view, the occurrence of a glioblastoma secondary to a meningioma most likely happens by chance. However, the coexistence of meningioma and glioma is the most common primary cerebral tumor association, mainly because of their respective incidences. Multiple intracranial tumors represent 4%–8% of all cerebral cancers. Approximately 8% of glial tumors occur in multiple locations concurrently, and the rate of multisite meningioma fluctuates from 1% to 6%. Nevertheless, the coexistence of meningioma and glioma in the same patient remains rare.

An alternate hypothesis for the cause of the coexistence of glioblastoma and meningioma may be surgery. The alteration of parenchyma after the surgery for the first meningioma could have caused glioma transformation. Indeed, there are published cases of post-traumatic glioma. The arachnoid membrane between the brain and meningioma is not always identified during surgery, which may lead to damage of the adjacent tissue. The 1-year minimum latency period required by Zuch’s diagnostic criteria for post-traumatic glioma confirms this possibility. Nevertheless, most of the patients with cranial trauma or surgical history do not develop secondary glioma. Subsequently, an additional agent could be involved in glioma
genesis. Thus, experimental data highlights that, in the presence of a neurocarcinogenic initiating agent, cranial trauma could contribute to the oncogenic process.\(^\text{19}\) In this manner, glial-cell injury surrounding a tumor lesion could induce the development of a secondary tumor, regardless of the histological type of the first lesion.\(^\text{5,20}\) In this case, when a glioma and a meningoima are in close proximity, either of the two could act as a neoplastic process-initiating agent. We could identify only isolated cases in a literature search, and we found no studies to confirm this hypothesis.

Conversely, on the basis of the oncogenic role of pluripotent embryonic cells, Cohnhelm’s theory supposes a genetic relationship between both these tumor types.\(^\text{5}\) This hypothesis has not been confirmed. Several single-nucleotide polymorphisms affecting DNA-repair ability and changing oncogenesis sensitivity have been depicted, with contradictory results depending on the study. A possible relationship between the XRCC1 and XRCC3 polymorphisms and the risk of developing meningioma and glioma (and more particularly glioblastoma) suggests a similar genetic susceptibility between these two tumors.\(^\text{21}\) We could not perform these genetic analyses on our patient because of the specificity of the material required and the lack of tumor samples. However, this does not explain the close proximity of the two tumors, which is observed in a third of all cases.\(^\text{5}\) One explanation could be the initial involvement of the cellular environment, and, more specifically, the activation of the signaling pathways demonstrated by immunohistochemical analyses. Glioblastoma and meningioma signaling pathways have several common abnormalities, including p53, receptor tyrosine kinase (RTK), Notch, and Wnt.\(^\text{22,23,24}\) Epidermal growth factor receptor (EGFR) expression, which is a component of the RTK pathway, has been reported in 20% of all benign meningiomas and is thought to be involved in gliomagenesis.\(^\text{22,24}\) Moreover, p53 mutation occurs in <5% of benign meningioma cases, in contrast to 19% of atypical meningioma cases and 70% of anaplastic meningioma cases.\(^\text{25}\) It is linked to vascular epidermal growth factor (VEGF) expression, and it is supposed to play an oncogenic role on the cellular and micro-environmental levels.\(^\text{25}\) Moreover, in a glial tumor with neuronal and oligodendroglial components without 1p/19q co-deletion, signaling molecules like PDGFR-a, PDGF-b, or p53 are believed to have an effect on tumorigenesis.\(^\text{24}\) In addition, proliferation rates of the two tumors suggest that the meningioma appears first, which then induces a glial transformation by p53 dysfunction and RTK activation.\(^\text{24}\) From all these assumptions, a low-grade astrocytic glial lesion could have existed initially next to the meningioma, which could have been overlooked and not biopsied. In compound injury cases, hyperintensity on fluid-attenuated inversion recovery (FLAIR)-balanced MRI sequences does not distinguish different tumor types. However, immunohistochemical study of p53 markers
and IDH1 mutations allows us to exclude this possibility. Indeed, p53 and IDH1 mutations are useful to differentiate a primary glioma from a secondary glioma. These tumors are found in 63% and 85% of all secondary glioblastoma cases, respectively, contrary to 28% and 5% of all primary glioblastoma cases, respectively.\textsuperscript{26,27} In our case, the low p53 positivity and the absence of IDH1 mutation favor the diagnosis of primary glioblastoma.

Table 1 reports all published cases of glioma and meningioma at a same location within the same individual (Table 1). Ohba describes a similar case of a glioblastoma occurring in a meningioma surgical site, which differs from ours by its longer time to onset after surgery. The molecular and chromosomal analyses of the glioblastoma were consistent with the primary lesion.\textsuperscript{4}

**CONCLUSION:**

The meningioma and glioblastoma's coexistence at the same site or in an adjoining area within an individual is still controversial. Nowadays, chance remains the most common explanation. Nevertheless, on the basis of several immunohistochemical studies, impairment of the same signaling pathways in these two tumor types could indicate a common origin. The potential oncogenic effects of the initial tumor or surgery on the adjacent tissue is an alternative hypothesis deserving further research.
**Figure 1**: Radiological and histological features of the initial tumor and lesion relapses

<table>
<thead>
<tr>
<th>(a): Brain T1-weighted gadolinium-enhanced MRI sequence, axial plane, of the initial lesion: Tumor lesion with left parietal localization, calcifications, dural basis, contiguous to meninges. Peripheral edema and homogeneous enhancement after gadolinium injection. Cranial vault destruction opposite the lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b): Histological results of the first sample: EMA (top) and GFAP (down) marking ×100: EMA marking &gt;75%. Ki-67 at 3%</td>
</tr>
<tr>
<td>(c): Brain T1-weighted gadolinium-enhanced MRI sequence, axial plane, of the first recurrence: Left parietal recurrence, with meningeal attachment. Peripheral edema and homogeneous enhancement after gadolinium injection.</td>
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<tr>
<td>(d): Histological results of the second sample: GFAP marking ×50: High expression of GFAP. Ki-67 at 25%</td>
</tr>
<tr>
<td>(e): Brain T1-weighted gadolinium-enhanced MRI sequence, axial plane, of the second recurrence: Repeat recurrence with left parietal edema infiltration and homogeneous enhancement after gadolinium injection.</td>
</tr>
<tr>
<td>(f): Histological results of the third sample: GFAP marking ×50: High expression of GFAP. Ki-67 at 25%</td>
</tr>
</tbody>
</table>

**ACKNOWLEDGEMENTS:**
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REFERENCES:


**Table 1:** Review of the literature concerning cases of meningioma and glioma at the same site within an individual.

<table>
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<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>56</td>
<td>47</td>
<td>75</td>
<td>72</td>
<td>79</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>F</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td><strong>Meningioma localization</strong></td>
<td>Right frontoparietal</td>
<td>Right parieto-occipital</td>
<td>Left temporal</td>
<td>Right frontal</td>
<td>Left parietal</td>
</tr>
<tr>
<td><strong>Meningioma management</strong></td>
<td>Complete resection</td>
<td>Complete resection</td>
<td>Complete resection</td>
<td>Complete resection</td>
<td>Complete resection</td>
</tr>
<tr>
<td><strong>Meningioma histology</strong></td>
<td>Unknown</td>
<td>Convex psammomatous meningioma</td>
<td>Meningiothelial meningioma</td>
<td>Meningiothelial meningioma</td>
<td>Grade-I fibroblastic meningioma</td>
</tr>
<tr>
<td><strong>Post-surgery recurrence time</strong></td>
<td>Unknown</td>
<td>15 months</td>
<td>Unknown</td>
<td>4 years</td>
<td>2 years</td>
</tr>
<tr>
<td><strong>Second lesion histology</strong></td>
<td>Oligodendroglioma</td>
<td>Grade-2 astrocytoma</td>
<td>Glioblastoma</td>
<td>Glioblastoma without IDH1 mutation</td>
<td>Glioblastoma without IDH1 mutation</td>
</tr>
<tr>
<td><strong>Glioma management</strong></td>
<td>Unknown</td>
<td>Radiotherapy and chemotherapy</td>
<td>Radiotherapy and chemotherapy according the STU PP protocol</td>
<td>Radiotherapy and chemotherapy according the STU PP protocol</td>
<td>Radiotherapy and chemotherapy</td>
</tr>
<tr>
<td><strong>Death time (since glioma diagnosis)</strong></td>
<td>Unknown</td>
<td>2 years</td>
<td>Unknown</td>
<td>Unknown recurrence at 7 months</td>
<td>14 months</td>
</tr>
</tbody>
</table>
HIGHLIGHTS:

- Glioblastoma and meningioma have same molecular-signaling-pathway impairments.
- Molecular-signaling-pathway impairments can indicate a common origin for tumors.
- Glial transformation due to radiotherapy or surgery could be causative.
- Primary tumor oncogenicity or surgical effect on adjacent tissues may be causative.