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Extensive leptomeningeal intracranial and spinal metastases in a patient with a supratentorial glioblastoma multiforme, IDH-wildtype: A case report

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Abstract

Background: Glioblastomas are usually characterized by diffuse, infiltrative growth and local tumor progression. Extensive leptomeningeal metastases are rarely observed. It remains unclear which GBMs are prone to this specific growth pattern/progression and standardized salvage treatment protocols are unavailable.

Case Description: A 45-year-old male patient without focal neurologic deficit was diagnosed with a right temporal glioblastoma, IDH (isocitrate dehydrogenase 1/2)-wildtype (biomarkers: O6-methylguanine-DNA-methyltransferase promoter methylation negative, Ki-67 proliferation rate 70%). Gross tumor resection followed by concomitant and adjuvant radio-/chemotherapy with temozolomide was performed. Routine follow-up imaging after eight months revealed a right, parietal, meningeal tumor. A resection confirmed a distant glioblastoma and next-generation sequencing revealed high tumor mutational burden, high frequency microsatellite instability and a pharmacologically targetable tyrosine kinase (KIT) mutation. Complete neuraxis imaging revealed multiple contrast-enhancing tumors in the craniocervical junction and levels C7, Th8-Th11 and S1. The craniocervical tumor formations and the cervical myelon from C1-2 were irradiated in palliative care intention and a second-line combined chemo-/ and antiangiogenic therapy with irinotecan and bevacizumab were initiated, and later changed to an immune-checkpoint blockade with pembrolizumab in combination with bevacizumab due to tumor progression. Hereunder tumor growth was slowed but eventually the patient developed a progressive paraparesis. A subsequent KIT-targeting tyrosine kinase inhibitor therapy with imatinib was short-lived and the patient eventually died 13.8 months after initial diagnosis.

Conclusions: High-risk genetic profiles for GBMs prone to develop extensive leptomeningeal metastases need to be identified. Guidelines on preemptive, complete neuraxis imaging in certain GBM patients and treatment guidelines have to be developed.
Keywords: Biomarker; Extracranial; Genetic profile; Glioblastoma multiforme; Leptomeningeal metastases; Outcome; Salvage treatment
Introduction

Glioblastoma multiforme (GBM) (WHO grade IV) is the most malignant primary brain tumor with patients’ overall survival rates in the range of 12 – 15 months.\(^1\) GBMs are characterized by diffuse, highly aggressive and infiltrative growth patterns usually leading to tumor progression and recurrence in close proximity to the initial site of tumor manifestation.\(^2\) Extensive leptomeningeal metastases/spreading and/or distant metastases in general, and spinal metastases in particular, of primary intracranial GBMs, however, are a rarely documented phenomenon, only observed in ~5% of all patients.\(^3\)-\(^7\) Thus, applicable salvage treatment protocols for those cases are very scarce.

We present the rare case of a patient suffering from a supratentorial GBM, IDH-wildtype, who developed extensive leptomeningeal intracranial as well as spinal metastases over the course of the disease. A detailed depiction of the patient’s signs and symptoms, radiological findings, the tumor’s histopathology and biomarker profile, as well as the applied salvage treatment is given.

Case Description

A 45-year-old, otherwise healthy, male, Caucasian patient was diagnosed with a 5 x 4 x 6.5 cm contrast-enhancing mass lesion with perifocal edema of the right temporal lobe after suffering from an episode of severe headache following physical strain; no focal neurologic deficits were documented at the time of the initial diagnosis (Fig. 1a; date of MRI: 09/2016). Due to the patient’s reports of suspected epileptic auras consisting of metallic taste sensations, an anti-epileptic drug regimen was established. A tumor resection was performed with histopathological analysis confirming a GBM, IDH (isocitrate dehydrogenase 1/2)-wildtype (biomarker profile: O6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation negative, focal Ki-67 proliferation rate of 70%). The postoperative course was uneventful; postoperative magnetic resonance imaging (MRI) revealed gross total tumor resection (Fig. 1b; date of MRI: 09/2016). Following surgery a concomitant radio-/chemotherapy (dose: 60Gy (2Gy per fraction/5 times weekly), temozolomide (TMZ) 75mg/m\(^2\)/daily) and adjuvant chemotherapy with TMZ (cycle 1: 150 mg/m\(^2\)/daily, cycle 2-6: 200 mg/m\(^2\)/daily) according to the EORTC-NCIC protocol was initiated.\(^1\)
Eight months after initial surgery a routine follow-up MRI scan revealed a distant right parietal, contrast-enhancing, meningeal tumor formation (1.8 x 0.9 x 1.5 cm) with beginning compression/infiltration of the central region while stable/regressive contrast enhancement at the right, temporal primary tumor location was observed; no new tumor-specific symptoms were recorded (Fig. 1c, date of MRI: 05/2017). A gross total resection of the right, parietal tumor was conducted which confirmed the tumor to be a distant manifestation of the known GBM, IDH-wildtype, with an even higher focal Ki-67 proliferation rate of 90% (Fig. 1d; date of MRI: 06/2017). Postoperatively, the patient was again found to suffer from no neurologic deficit. However, postoperative cranial MRI showed multiple small, contrast-enhancing, nodular lesions around the left foramen Luschkae and ventrally of the medulla oblongata (Fig. 2a and 2b; date of MRI: 06/2017). Due to the histopathology and craniocervical spreading, an MRI scan of the whole neuraxis was additionally performed which revealed multiple spinal extraaxial contrast-enhancing tumors at levels C7, Th8-Th11 and S1. Due to beginning ataxia and in order to avoid a consecutive hydrocephalus occlusus, it was decided to irradiate the tumor formations located in the left cerebellar penduncle, the adjacent brain stem as well as the cervical myelon including C1 to C2 (30 Gy/3 Gy per fraction) in a palliative care intention. This was followed by a second-line antibody/-chemotherapy regimen consisting of bevacizumab (10 mg/kg every 2 weeks) and irinotecan (125 mg/m² every 2 weeks) (Fig 2c; date of MRI: 08/2017). Over the following two months, the patient developed vertigo and a mild, progressive gait ataxia. Follow-up MRI scans confirmed spinal tumor progression (Fig. 2d; date of MRI: 09/2017). Subsequently, the patient’s condition stabilized; the patient was still physically active by jogging up to 50 km per week and the palliative systemic treatment was well tolerated. Short-term MRI scans, however, showed further tumor growth and next generation sequencing studies (Foundation One®, Foundation Medicine, MA, USA) were performed; the patient had given informed consent to participate in the “NGS registry“ of the Arbeitsgemeinschaft Medikamentöse Tumortherapie (AGMT; Working Group for Drug Tumor Therapy). Several genomic alterations (ataxia telangiectasia mutated (ATM), breast cancer 2 (BRCA2), Fibroblast growth factor receptor 1 (FGFR1), tyrosine-protein kinase (KIT), mitogen-activated protein kinase kinase 1 (MEK1), transmembrane tyrosine kinase receptor (MET), neurofibromatosis 1 (NF1), Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), phosphatase and tensin homolog (PTEN);
smoothened, frizzled class receptor (SMO), and tumor protein p53 (TP53)) as well as a high tumor mutational burden (TMB-High) and a high frequency microsatellite instability (MSI-High) with potential therapeutic implications were identified. Details on the documented genetic alterations are displayed in tables 1 and 2. Due to the TMB-High and MSI-High status the salvage treatment was modified to a combined immune-checkpoint blockade and anti-angiogenic therapy with pembrolizumab (200mg every 3 weeks) and bevacizumab (10mg/kg every 2 weeks) as an individualized treatment attempt.\textsuperscript{9-11} This was able to stabilize the patient’s condition for another two months. Nonetheless, the patient’s condition then rapidly worsened by developing a progressive paraparesis and disorientation. As the patient’s GBM harbored a KIT\textsuperscript{D737N} mutation, targeted therapy with the oral tyrosine kinase inhibitor imatinib mesylate was initiated, but was short-lived due to further clinical deterioration and the treatment concept was switched to best supportive care.\textsuperscript{12} The patient eventually succumbed to the disease 13.8 months after the initial diagnosis; the initial time to progression with development of distant metastases was 8.7 months.

Discussion

In this case report, we provide a detailed description of a patient suffering from extensive intracranial and spinal leptomeningeal metastases of a supratentorial GBM, IDH-wildtype, as well as the salvage treatments applied over the course of the disease.

Salvage treatment of recurrent/progressive GBMs is still mostly based on individualized decisions since clear recommendations remain scarce.\textsuperscript{13} This, of course, is especially true for the rare cases with spinal leptomeningeal metastases for which sufficient data are lacking and appropriate experiences are only available in form of retrospective case series.\textsuperscript{4-7,14-20} When analyzing the available literature, the most commonly proposed mechanism for development of spinal GBM spreading appears to be the via leptomeningeal route and cerebrospinal fluid (CSF) seeding. Thus, opening of the ventricle during glioma surgery is usually regarded to negatively affect patients’ outcome and should therefore be avoided whenever possible. Notably, however, Behling et al. recently reported that in a series of 229 GBM patients they did not find ventricular opening during surgery to be an independent predictor for overall survival and, thus, recommended opening of the ventricle to
achieve gross total resection.\textsuperscript{21} No data, however, on consecutive intraventricular tumor spreading is provided, which hereby limits further informative impact on the decision-making process. On the other hand, Dardis et al. did report a proximity of the tumors’ primary location to the lateral ventricle in 50\% of their analyzed patients with leptomeningeal spreading gliomas; thereby, possibly indicating the origin of the tumor by itself being a risk factor for development of leptomeningeal metastases.\textsuperscript{4} In accordance to this finding, our patient’s initial tumor formation of the right temporal lobe had already infiltrated the sub-/ependymal layer of the ventricular temporal horn, thereby possibly facilitating a spread via the CSF route. Thus, during the patient’s initial surgery, the ventricle had to be minimally opened in order to achieve gross tumor resection. The correlation between spatial proximity to (i.e. temporal lobe and corpus callosum tumors) or infiltration of the ventricular system by the intracranial tumor and the development of spinal metastases has also been observed by other authors.\textsuperscript{4,6,14,15,18,20} Spinal metastases of malignant brain tumors such as anaplastic ependymomas and medulloblastomas are a rather frequent complication, and MRI scans of the complete neuraxis have become a standard investigation to be performed in all affected patients. It remains unclear, however, why even GBMs with involvement of ventricular system do usually not cause spinal drop metastases.

Genetic biomarker profiling has become a keystone feature of modern neuro- oncology and has led to a continuous, improved understanding of the tumors’ biology as well as prognosis and response to treatment. Understanding of genetic associations, which may facilitate metastasizing/spreading in GBMs, however, are still largely unknown. Most published cases on spinally metastasized GBMs do not even mention the tumors’ biomarker status.\textsuperscript{6,14-16,18,20} Nonetheless, Korshunov et al. reported that genetic alterations of chromosome arm 1p36 were found to be associated with leptomeningeal dissemination of supratentorial GBMs, and Schindler et al. described genetic gains and losses on chromosomes 7, 10 and 13 in a case of a spinally metastasized GBM.\textsuperscript{22,23} Furthermore, mutations of the tumor suppressor gene PTEN have been assumed to favor dissemination of GBMs.\textsuperscript{24} Our patient suffered from a prognostically unfavorable, intracranial GBM, IDH-wildtype (MGMT promoter methylation negative) with an extremely high focal Ki-67 proliferation index as well as a high tumor mutational burden at the time of spinal dissemination. Next generation sequencing (NGS) was performed on both, the temporal as well as the parietal, tumor tissues. In our patient’s case, the NGS analyses revealed that a
number of genes were carrying mutations. Mutations in some genes (i.e. PIK3CA, SMO, and TP53) were detected in the tumor specimens of both operations while mutations of other genes (i.e. PIK3CA, RB1, TP53, and VHL) were detected in tumor specimens obtained upon one surgical intervention. These diverging results can be explained by the heterogeneity of the tumor tissue and the resulting clonal heterogeneity of tumor cells. The molecular subtyping of GBM especially of recurrent GBM as proposed by Sturm et al. may therefore not be adequate. Thus, the crucial aspect of molecular tumor characterization definitely deserves more attention in future cases and studies.

The time span between the initial intracranial tumor manifestation and the occurrence of spinal metastases most commonly appears to be in the range of 1 – 16 months. Affected patients usually become symptomatic due to compression or infiltration of the spinal cord and/or nerve roots; patients may suffer from sciatica, gait ataxia/paresis, sensory deficits and bowel/bladder dysfunction. In our case, the spinal leptomeningeal spreading was discovered rather early by a routine follow-up MRI including the craniocervical junction with ataxia as main symptom at this point of time. Furthermore, even though the tumors continued to grow during salvage treatment, the patient did not develop severe spinal symptoms until two months before his death.

In our patient, we decided against resections of any spinal tumor manifestation due to the lack of any specific, attributed symptoms as well as the sheer, multiplicity of the lesions. Nonetheless, depending on the patient’s general condition, the dimension of systemic disease as well as specific symptoms due to extramedullary tumor formations a local resection and/or radiotherapy with consecutively intensified systemic or intrathecal chemotherapy can be considered as salvage treatment according to the assessed biomarker status. Based on our patient’s hypermutational tumor status, we opted for an immune-checkpoint inhibitor therapy with pembrolizumab in combination with bevacizumab based on the TMB-H and MSI-H status and a previous report on the safety of this combination in recurrent GBM. With a range of 0-8% the reported frequency of MSI-H GBM is low but checkpoint inhibitors have shown promising results in hypermutated cancers and have recently gained increasing interest in the treatment for malignant gliomas. KIT mutations and amplifications are detected in 1% and 9% of GBM, respectively. Unfortunately, targeted therapy of the identified KIT<sup>D737N</sup> did not derive any benefit in our patient.
The overall dismal nature of the underlying disease, extensive leptomeningeal metastases as well as patients’ poor general condition should be regarded as contraindications to any microsurgical treatment. Moreover, we believe that symptomatic and asymptomatic metastases of a glioblastoma should be regarded as two different clinical entities of the disease with regard to the treatment and patient counseling. Besides the clinical symptoms, however, we believe that other important factors that have be additionally considered for any treatment decisions should be (1) the general extent of the tumor progression (i.e. number of symptomatic and asymptomatic tumors), (2) the size of the tumor (e.g. imminent danger of development of clinical symptoms due to compression/infiltration of eloquent brain region or blockage of CSF circulation/hydrocephalus), (3) as well as the patients’ preferences in view of the overall dismal prognosis of the disease. As in all patients with progressive GBMs, we believe that maintaining the neurological status and quality of life for as long as possible should dictate any treatment decisions, whether it be salvage treatments or initiation of palliative/best supportive care.

Overall, data on extensive leptomeningeal metastases in GBM patients are sparse, mainly due to its rarity. A major future goal has to be to preemptively identify patients at high risk for development of spinal and/or distant tumors based on their tumors’ specific genetic profiles, which might trigger or promote such growth patterns. Complete neuraxis imaging protocols for these patients ought then to be to routinely implemented and corresponding standardized treatment algorithms have to be developed.

Conclusions

Data on extensive leptomeningeal metastases of patients with primary intracranial GBM remain scarce. Therefore, it is unknown whether tumors with certain characteristics (i.e. locations, genetic biomarker profiles) are more prone to this specific growth pattern/tumor progression. Future studies should put more emphasis on the identification of possible risk factors with special focus on the tumors’ distinct genetic profiles, which are associated with a higher risk for the development of spinal GBM spreading. Based on the findings, guidelines on preemptive, complete neuraxis imaging in certain “high-risk” GBM patients as well as treatment guidelines for leptomeningeal tumor spreading need to be developed. Due to the limited prognosis
of patients with multilocular, progressive GBMs, we believe that maintaining the neurological status and quality of life for as long as possible should dictate any salvage treatment decisions.

Conflict of Interest: The authors declare that there is no conflict of interest.

Figure legends

Fig. 1a: Preoperative post-contrast T1 sequence revealed a garland-shaped contrast-enhancing right temporal, central necrotic lesion with contact to the right temporal horn (histologically confirmed GBM, IDH-wildtype) (date of MRI: 09/2016)

Fig. 1b: Postoperative MRI reveals no contrast-enhancement after gross total resection of the right temporal tumor (date of MRI: 09/2016)

Fig. 1c: Eight months later, a leptomeningeal contrast-enhancing tumor spread lesion appeared right parietal (date of MRI: 05/2017)

Fig. 1d: After gross total resection of the secondary parietal lesion no contrast-enhancing residues can be detected on postoperative MRI scans (date of MRI: 06/2017)

Fig. 2a and 2b: Extensive craniocervical and spinal metastases of the GBM was detected on neuraxis scans shortly after the second surgery (date of MRI: 06/2017)

Fig. 2c: Shrinking of the craniocervical metastasis under salvage radio-/chemotherapy (date of MRI: 08/2017)

Fig. 2d: Tumor progression of the multiple thoracic extramedullary tumor formations (date of MRI: 09/2017)
References


Table 1: Detailed genetic alterations

<table>
<thead>
<tr>
<th>Gene name:</th>
<th>Amino acid mutation:</th>
<th>Variant allele frequency (VAF):</th>
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<tbody>
<tr>
<td>PIK3CA</td>
<td>C420R</td>
<td>24.4%</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Q1033</td>
<td>21.7%</td>
</tr>
<tr>
<td>SMO</td>
<td>A324T</td>
<td>26.2%</td>
</tr>
<tr>
<td>FGFR1</td>
<td>N272D</td>
<td>26.6%</td>
</tr>
<tr>
<td>TP53</td>
<td>R273C</td>
<td>27.9%</td>
</tr>
<tr>
<td>TP53</td>
<td>A161T</td>
<td>27.3%</td>
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<tr>
<td>ATM</td>
<td>T2853M</td>
<td>1%</td>
</tr>
<tr>
<td>BRCA2</td>
<td>splice site 9117+1G&gt;T</td>
<td>0.4-1%</td>
</tr>
<tr>
<td>KIT</td>
<td>D737N</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>MEK1</td>
<td>D67N</td>
<td>&lt;0.5%</td>
</tr>
<tr>
<td>MET</td>
<td>T1173I</td>
<td>0.4%</td>
</tr>
<tr>
<td>NF1</td>
<td>Q209*</td>
<td>9-14%</td>
</tr>
<tr>
<td>PTEN</td>
<td>N323fs*21</td>
<td>7.4%</td>
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Table 2: Comparative next generation sequencing results

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<th>Gene name:</th>
<th>1st surgery (temporal)</th>
<th>2nd surgery (parietal)</th>
</tr>
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<tbody>
<tr>
<td>PIK3CA</td>
<td>c.1258 T&gt;C</td>
<td>c.1258 T&gt;C</td>
</tr>
<tr>
<td>PIK3CA</td>
<td></td>
<td>c.3097 C&gt;T</td>
</tr>
<tr>
<td>RB1</td>
<td>c.1654 C&gt;T</td>
<td></td>
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<tr>
<td>SMO</td>
<td>c.970 G&gt;A</td>
<td>c.970 G&gt;A</td>
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<tr>
<td>TP53</td>
<td>c.817 C&gt;T</td>
<td>c.817 C&gt;T</td>
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<td>TP53</td>
<td>c.1010 G&gt;A</td>
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<td>TP53im</td>
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<td>c.481 G&gt;A</td>
</tr>
<tr>
<td>VHL</td>
<td>c.435 G&gt;T</td>
<td></td>
</tr>
<tr>
<td>FGFR1</td>
<td>c.814 A&gt;G</td>
<td>c.814 A&gt;G</td>
</tr>
</tbody>
</table>
Highlights:

- Leptomeningeal metastases are a rarely observed phenomenon in glioblastoma patients.
- It remains unclear which tumors are especially prone to leptomeningeal metastases.
- Future studies should focus on the identification of risk factors (i.e. tumor location, biomarkers) typical for this specific growth pattern/tumor progression.
- Neuraxis imaging protocols for patients at risk ought to be implemented and standardized treatment algorithms have to be developed.
Abbreviations: Ataxia telangiectasia mutated, ATM; Breast cancer 2, BRCA2; Cerebrospinal fluid, CSF; Fibroblast growth factor receptor 1, FGFR1; Glioblastoma multiforme, GBM; Isocitrate dehydrogenase, IDH; Tyrosine-protein kinase, KIT; Mitogen-activated protein kinase kinase 1, MEK1; Transmembrane tyrosine kinase receptor, MET; O6-methylguanine-DNA-methyltransferase, MGMT; MRI, Magnetic resonance imaging; Microsatellite instability, MSI; Neurofibromatosis 1, NF1; Smoothened, frizzled class receptor, SMO; Temozolomide, TMZ; Tumor mutational burden, TMB; Tumor protein p53, TP53; Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic cubunit alpha, PIK3CA; Phosphatase and tensin homolog, PTEN