Abnormal Schwannoma-like Growth of multiple, multifocal BRAF V600E-positive Glioblastoma in the Interior Acoustic Canal with Leptomeningeal Infiltration: a case report

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Abstract

Background: Glioblastoma (GB) is among the most common as well as most aggressive tumors of the central nervous system, and has a poor prognosis [1–4]. The incidence in the European Union and North America is 2–3/100,000 per year with slightly higher incidence in men. The highest rate of new diagnosis occurs in late adulthood at a median age of 64 years but it can also occur in children.

Conclusions: Glioblastoma rarely presents with metastases despite its aggressive and rapidly growing nature. Our case should increase awareness of symptom tracking in patients with glioblastoma to intervene early and efficiently. Moreover, refractory therapies for glioblastoma should underline the importance of personalized medicine.

Keywords: Epithelioid glioblastoma, Neuroradiology, Multiple glioblastoma, Neuro-oncology, Metastasized glioblastoma, Case report, BRAF

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Background

Glioblastoma (GB) is among the most common as well as most aggressive tumors of the central nervous system, and has a poor prognosis [1–4]. The incidence in the European Union and North America is 2–3/100,000 per year with slightly higher incidence in men. The highest rate of new diagnosis occurs in late adulthood at a median age of 64 years but it can also occur in children.
at any age [5–7]. Predominantly, GB appears as a unilateral, solitary lesion, whereas primary multiple, especially bilateral, lesions are rare [8–13]. Likewise, cases of GB with schwannoma-like growth are exceptional [14–16].

The spreading of GB presumably occurs via the cerebrospinal fluid to the ventricular cavity with successive dissemination throughout the ventricular system and cerebrospinal leptomeninges [13]. Interestingly, intracranial GB infiltrating leptomeninges and causing meningitis glioblastoma per se is rare [8, 17–19]. Metastasis of GB to the surrounding and contralateral brain parenchyma and to the extracranial tissue, with common sites being lungs, pleura, bones, bone marrow, skin, and cervical lymph nodes, has been observed [20–28]. The prevalence of extracranial metastasis is around 0.5%. However, metastases are more common in patients with recurrent disease than in patients at initial diagnosis [10, 13, 29–32]. Although recent research has introduced promising molecularly targeted compounds, one of the standard treatments utilizes temozolomide with simultaneous radiotherapy [33–39].

Case presentation

A 60-year-old Caucasian male was admitted to the emergency unit upon having a seizure, with no significant medical history. He reported a 2-month history of numbness in the left hand and intermittent dysarthria. Physical examination showed impaired fine motor skills and hypoesthesia in the left arm. Cranial magnetic resonance imaging (cMRI) revealed a multifocal 38 × 42 × 38 mm lesion in the right temporal lobe (Fig. 1a) and a singular lesion in the left internal auditory canal (IAC) with a discreet hyperintense signal and abnormal enhancement (Fig. 1b). Gross resection of the lesion in the right temporal lobe was performed. Immunohistopathological analyses identified the lesion as an isocitrate dehydrogenase (IDH) wild-type epithelioid glioblastoma with O6-methylguanine-DNA methyltransferase (MGMT) methylation at 12% and BRAF V600E mutation (Fig. 3). The patient was started on adjuvant concomitant chemoradiotherapy that included temozolomide [75 mg/m² body surface area (BSA), d1–d42] and stereotactic radiotherapy (60 Gy split in 30 units) of the tumor cavity in the right temporal lobe.
lobe and its marginalizing solid components [33]. The enhancement in the left IAC (Fig 1c) was not irradiated as the signal alteration was not interpreted as a metastasis [33]. To assess the therapy outcome, a cMRI was done on therapy day 42. The cMRI showed that the right-sided tumor cavity, including its solid components, remained unchanged in size but with a larger perifocal edema that was presumably a postradiogenic effect. However, the lesion in the left IAC excluded in the irradiation field was progressive (Fig. 2a). The oligoprogression prompted us to continue with temozolomide treatment at 100 mg/m² BSA as maintenance therapy. Within 2 weeks, the patient was seen in the outpatient oncology clinic with a marked imbalance, as well as a new, rapidly advancing left-sided facial nerve weakness, dysphagia, dysarthria, and left-sided deafness albeit without lower central nervous dysfunction. The Romberg test was positive, and his gait was wide and ataxic, with assistance required to prevent falling during tandem walking trials. These symptoms were consistent with the lesion in the left IAC. Due to the fast deterioration and a fall leading to a nose bone fracture, we admitted the patient to our clinic. Owing to the persistent dysphagia, we decided to implant a percutaneous endoscopic gastrostomy (PEG) tube to avoid aspiration and malnutrition. Four weeks following the adjuvant chemoradiotherapy, the cMRI demonstrated a rapid growth of the lesion in the left IAC. This lesion measured 31 × 24 × 33 mm and infiltrated the adjacent structure, that is, the cranial nerves (II, V, VII–XII), the leptomeninges, and the left parotid gland (Figs. 2b, 3). In addition, the meninges of the Sylvian fissure showed an enhanced contrast uptake that breached the left orbit and cerebellum with suspicious infiltrations into the medulla oblongata. Moreover, the tumor cavity with its solid residues in the right temporal lobe was accompanied by an expanding edema (figure not shown). A lumbar puncture was performed and confirmed meningeosis glioblastoma on cytopathological analysis. Laboratory tests showed that hematological and organ functions were not impaired. To control the impact of the expanding intracranial mass, we initiated radiotherapy of the whole brain. As the patient deteriorated fast, we could neither start the patient on second-line therapy, such as antiangiogenic drugs or BRAF V600E inhibitors, nor recruit him in a clinical trial. The approval of BRAF inhibitors for treating V600E-mutated epithelioid GB was pending at the time (Swissmedic National Authorization for Drugs, cited September 2020); it would therefore have been an experimental approach. We decided to dispense further diagnostics and did not perform a biopsy of the left intrameatal lesion. At the request of the family and the patient, we focused on palliative care. The patient died 4 months after the initial diagnosis owing to the rapid tumor progression that led to paralyses of multiple cranial nerves. The family did not wish for an autopsy.

Discussion
Multifocal GB is a highly aggressive and fast-growing tumor entity known for its poor prognosis and fatal complications. Typically, GB manifests as a single lesion, whereas multiple and particularly contralateral lesions are limited to only a few case reports [9, 10, 12]. One might suspect the short prognosis does not allow sufficient time for metastases to become clinically evident. In addition to the intracranial metastases of GB, intramedullary spinal metastasis, leptomeningeosis glioblastoma, and extracranial metastases are also very uncommon [8, 28, 31, 40–43]. Several mechanisms for metastasis have been postulated, including vascular invasion, perineural spreading, and direct invasion via the lymphatics [13].

In our case report, we describe a rare, abnormal primary bilateral manifestation of multiple,

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Fig. 2 Brain magnetic resonance imaging of lesions in the left internal acoustic channel advancing with schwannoma-like growth 2 and 4 months after diagnosis. a T1-weighted cranial magnetic resonance imaging after contrast showing the tumor in the left internal acoustic channel at 2 months post-surgical follow-up. b T1-weighted cranial magnetic resonance imaging after contrast revealing infiltrative tumor growth with suspicious leptomeningeal involvement in the cerebellopontine angle within 4 months after diagnosis. Right nasal fracture upon fall is shown.
multifocal BRAF V600E-positive intracranial epithelioid GB lesions in both hemispheres that subsequently advanced rapidly and invaded the left internal acoustic meatus with perineural infiltration of the adjacent cranial nerves and leptomeninges while the adjuvant chemoradiotherapy was ongoing. In the continuous clinical assessments, the patient developed symptoms that resembled those of a benign schwannoma, which is a slow-growing and noninvasive tumor of the peripheral nervous system. To date, only a handful of clinical reports of primary glioma lesions mimicking a schwannoma have been reported [15]. However, the patient’s poor performance did not permit a biopsy of the intrameatal lesion to examine its etiology. As the baseline cMRI disclosed abnormal signal alterations in the left meatus, we cannot exclude metastatic growth. Therefore, we might assume that the intrameatal lesion was a metastasis of epithelioid GB. Moreover, its fast growth over a few weeks attests to the typical tumor biology of GB.

Moreover, the radiological findings implied an infiltration of the leptomeninges that might have caused a meningeosis GB. Recent literature describes the occurrence of meningeosis GB in patients with spinal metastases [41, 44–49]. In our patient, we cannot exclude spinal metastases since we did not obtain a scan of the spinal cord owing to the rapid deterioration of the patient. However, the patient did not experience neurological symptoms that were typical of spinal metastases such as paralyses, radicular pain, or peripheral sensory impairment. Clinical signs of meningitis were too vague to draw any conclusions.

Recommendations for the clinical management of highly progressive and metastasized GB are scarce, making palliative care the remaining option [1]. Radiotherapy is the preferred choice to control intracranial mass effect and to improve neurological symptoms, while second-line chemotherapy shows no survival benefit. Surgical intervention is necessary if compression increases the intracranial pressure [30, 41, 48]. With precision medicine becoming the state of the art, several promising molecular targeting therapeutics are under investigation. For example, the role of driver mutations, such as BRAF and its effect on pathogenesis of CNS tumors, has recently gained special interest [39]. In classic GB, BRAF mutations are rare, while the prevalence is higher in epithelioid GB (prevalence 1–2% versus 50%, n = 1320 samples) [50].

With the evolving era of personalized medicine, Kaley et al. identified the BRAF mutation as a promising druggable molecular target in CNS tumors by conducting the basket trial VE-BASKET [51]. BRAF mutation is known to negatively influence the overall prognosis in several tumor indications, for example, malignant melanoma, papillary thyroid cancer, and so on [52]. Hence, GB harboring a BRAF V600E mutation might exhibit a different, more invasive tumor biology than that of a BRAF wild-type GB. In our case, the V600E-positive epithelioid GB was also refractory to therapy as tumor progression occurred during combined

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**Fig. 3** Histopathological analyses of the resected glioblastoma. a Histopathological specimen showing nuclear pseudopalisading, which is defined as the aggregation of tumor cells around the periphery of the necrotic areas, increased mitotic activity, and vascular proliferation. Pseudopalisading necrosis and vascular proliferation are the two important hallmarks of glioblastoma [53]. Magnification, 20×. b Histopathological specimen depicting an accumulation of viable tumor cells encircling the blood vessels in a large necrotic focus. The image also shows endothelial multilayering as a result of endothelial hyperplasia. These changes are mostly driven by vascular endothelial growth factor secreted by the tumor in response to hypoxia. Magnification, 20×.
chemoradiotherapy [33]. Here, the intratumoral heterogeneity might explain the treatment resistance of GB [53]. Certainly, cases of resistance to therapy should also encourage precision medicine research to establish novel algorithms for the treatment of GB [39, 50, 51, 54].

Currently, the data on the effect of BRAF inhibitors (BRAFi) on BRAF V600E-positive brain tumors are limited to a few experimental studies and case reports; thus, there is a high demand for further investigation. So far, the treatment of different types of brain tumors with BRAFi prolonged survival by several months to several years [37, 54]. Undoubtedly, response rates depend on the type of CNS tumor and tumor load [34–36, 38].

Conclusion

Though our case is a rare observation, multiple metastases can lead to lethal tumor progression within days to weeks. Our study highlights several take-home messages: firstly, the clinician should focus on symptom tracking in patients with GB, so that symptoms that cannot be explained by the primary GB manifestation are recognized earlier. With these basic clinical assessments, an intervention can be planned efficiently. Symptom tracking might be extended with selected disciplines such as otolaryngology, neurology, and ophthalmology. Secondly, the future development of personalized cancer medicine should focus on molecular signatures, thereby introducing potential druggable targets. Besides molecular targeting compounds, immunotherapies are highly promising options, that is, T-cell therapies [chimeric antigen receptor T cells (CAR-T), tumor-infiltrating lymphocytes (TILs) and bispecific T-cell engagers (BiTEs)]. In particular, cases of refractory therapies necessitate the development of novel therapeutic algorithms. Finally, yet importantly, our case alludes to rare cases and their radiological presentation, thus improving the diagnostic workup overall. Should the left-sided lesion be regarded as a potential metastasis, a different therapy approach should be planned, for example, whole-brain rather than stereotactic radiotherapy.

Abbreviations

GB: Glioblastoma; Gy: Gray; IAC: Internal acoustic channel; BRAFi: BRAF inhibitors; BSA: Body surface area; BRAF: Rapidly accelerated fibrosarcoma isoform B; GB: Glioblastoma; Gy: Gray; IAC: Internal acoustic channel; BRAFi: BRAF inhibitor.

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Authors’ contributions

Material preparation, data collection, and analysis were performed by R.J.N. and E.G. The first draft of the manuscript was written by R.J.N., and both authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Yes.

Declarations

Ethical approval and consent to participate

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Consent was collected when tumor extirpation for pathological analyses was done.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no conflict of interest or any disclosures.

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