





SHORT COMMUNICATION

Loss of IDH mutation or secondary tumour manifestation? Evolution of an IDH-mutant and 1p/19q-codeleted oligodendroglioma after 15 years of continuous temozolomide treatment and radiotherapy: A case report

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Chemotherapy plays a vital role in the management of various diffuse gliomas. Temozolomide (TMZ) or procarbazine, lomustine and vincristine (PCV) are commonly administered drugs in neuro-oncology. TMZ is routinely applied in 1p/19q-intact gliomas. In 1p/19q-codeleted, isocitrate dehydrogenase (IDH)-mutant (IDH^{mut}) oligodendrogliomas, PCV is considered the standard of care, with only emerging data concerning TMZ administration. Glioma recurrences after chemotherapy, however, exhibit specific mutational alterations [1]. In cases treated with TMZ, recurrences may demonstrate mutations that disable

mismatch repair (MMR) pathways and ultimately result in a hypermutated tumour with the likelihood of malignant transformation [1, 2]. Furthermore, the treatment of gliomas usually includes surgery, radiotherapy and radiochemotherapy (RCT). Radiotherapy is known to promote secondary gliomagenesis [3, 4]. The majority of such tumours arise approximately 10 years after radiotherapy as high-grade gliomas [3]. The occurrence of oligosarcomas, a rare and aggressive entity, has also been described after the treatment of oligodendroglial tumours [5]. We describe the case of a patient that was misdiagnosed with a glioblastoma (GB) instead of oligodendroglioma and was ultimately treated with continuous TMZ for more than 15 years. Eventually, the

Josefine Radke and David Kaul contributed equally to this work.

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patient suffered from a second malignant glioma, which exhibited distinct and different molecular features.

At the age of 16 years, the male patient suffered from his first generalised seizure. To this date, his medical history was only notable for depression. He underwent magnetic resonance imaging (MRI, not available), which was suggestive of a left-sided frontoparietal low-grade glioma and a cavernoma in the left parietal lobe. Given the seizure without other pertinent findings, the glioma was identified as the most probable underlying cause. Given the age of the patient and fear of complications, the parents declined surgical biopsy or resection of the tumour and chose a watch-and-wait approach. Over the following 12 years, the patient suffered from a few seizures without any signs of tumour progression. After an increasing frequency of seizures, a stereotactic biopsy was recommended to rule out malignant transformation (Figure 1A). Until this point, no tumour progression was seen on follow-up imaging since the initial diagnosis. A first biopsy did not contain enough tumour tissue for sufficient histopathological evaluation.

At the age of 29, the MRI of the head (not available) showed a new intensified peripheral contrast enhancement of the tumour. At that time, the tumour was resected and histologically classified as GB based on microvascular proliferation and beginning necrosis. The patient underwent RCT, with a total dose of 60 Gray (Gy) and six cycles of TMZ. Upon treatment completion and after informed consent, the treating physician decided to continue medication with further cycles of TMZ. Subsequently, the patient received a total of more than 180 continuous TMZ cycles. During these 15 years, no significant myelosuppression or other significant adverse events were observed. The patient underwent regular follow-up imaging with contrast-enhanced MRI.

However, a follow-up MRI in the 16th year of TMZ administration demonstrated a new lesion with peripheral contrast enhancement and a necrotic core located in the left trigone of the ventricle's occipital horn suggestive of a GB recurrence (Figure 1B). This lesion was located at the posterior resection border of the tumour, which was initially resected before TMZ therapy. The patient subsequently underwent surgical resection. Further immunohistochemical and molecular analyses revealed an IDH wild type (IDH^{wt}) tumour with homozygous deletion of the cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*) and platelet-derived growth factor receptor A (*PDGFRA*) amplification, but without 1p/19q-codeletion (Figure 1F–H,J). The tumour was not classifiable, using version v11b4 of the DNA methylation-based brain tumour classifier (calibrated score 0.74 for “methylation class family Glioma, IDH mutant”, calibrated score 0.71 for the subclass “high grade astrocytoma”, Figure 1J) [6].

Epigenetic profiling of the specimen from the first resection was conducted to elucidate the relation between both lesions. Surprisingly, this tumour was classified as an oligodendroglioma, IDH^{mt} and 1p/19q-codeleted (calibrated score 0.99, Figure 1C–E,I). The *IDH1* R132H mutation was validated by immunohistochemistry and pyrosequencing (Supporting Information S1). The copy number variation data obtained from 850k/*EPIC* Illumina methylation assays (Illumina Inc., San Diego, CA, USA) demonstrated a 1p/19q-codeletion and

Key Points

- Oncogenic drivers in glioma may change throughout the course of the disease and in the context of tumour progression.
- Additional molecular diagnostics, that is, DNA methylation analysis, are strongly recommended in patients with unusual treatment courses and multiple brain tumours.
- Secondary gliomagenesis after radiochemotherapy remains a significant problem in long-term brain tumour survivors and is still poorly understood.

homozygous *CDKN2A/B* deletion, as well as a chromosome 4 monosomy (Figure 1I). To further clarify the molecular profile and possible evolution of the tumour, we analysed the DNA obtained from the tissues during the first biopsy and both surgical resections using next-generation sequencing (i.e., Intracranial Tumour Panel ICT 1.0). Common mutations in all three tissues were the telomerase reverse transcriptase (*TERT*) promoter mutation C228T and a pathogenic frameshift mutation in the *TSC1* gene (p.(N891Kfs*13), Table 1). Interestingly, the mutant allele frequency (MAF) of *TERT* decreased from 31% to 2% (Table 1). At the beginning, the tumour had gained a *CIC* p.(R215W) mutation and revealed chromosome 4 monosomy, which—together with the *IDH1* p.(R132H) mutations and 1p/19q codeletion—was not detectable at recurrence. This tumour demonstrated a pathogenic *PIK3CA* p.(M1043V) mutation, while both resected tumours showed methylation of the O⁶-methylguanine-DNA-methyltransferase (*MGMT*). The patient received another course of RCT for the malignant IDH^{wt} glioma with a total dose of 59.2 Gy. TMZ was continued afterwards but several hospitalizations occurred due to extensive nausea. Less than 6 months after the second RCT, the patient ultimately succumbed to his disease—more than 28 years after his initial brain tumour diagnosis.

Despite the comprehensive retrospective molecular profiling, it remains unclear how the final malignant glioma, IDH^{wt}, developed. Possible explanations comprise the lineage conversion and dual genotype theory, the independent de novo development of the malignant glioma, and secondary tumorigenesis due to the extensive TMZ administration and previous RCT.

In general, lineage conversion describes a genetic switch of the initially found tumour type to another. However, loss of IDH mutation—the supposed oncogenic driver alteration—seems to be an extremely rare observation [7]. To the best of our knowledge, this has not been described in oligodendroglioma thus far. As pointed out by Touat et al., IDH mutations in astrocytomas, however, may be substituted by other, stronger oncogenic drivers throughout the course of the disease and in the context of tumour progression [7]. So far, case reports of oligodendroglioma changing their 1p/19q codeletion status throughout the course of the disease have been rarely

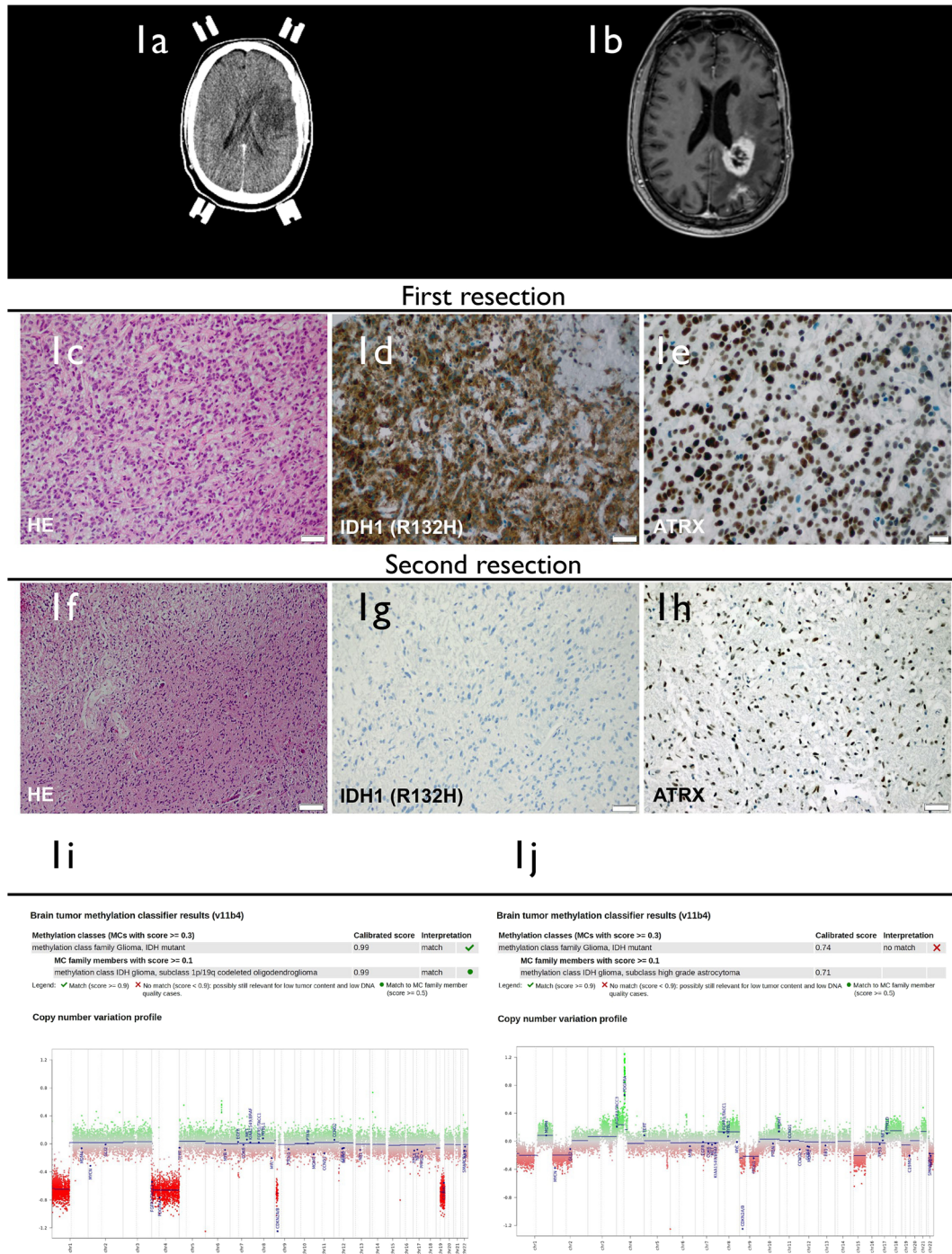


FIGURE 1 (A) Computed tomography in preparation of the first stereotactic biopsy, axial plane. The progressive tumour is located in the fronto-parietal and insular region of the left cerebral hemisphere and causes surrounding oedema. (B) Magnetic resonance imaging, T1 contrast-enhanced, axial plane. A new contrast-enhancing lesion with a suggested necrotic core was identified at the posterior resection border of the initially resected tumour. The lesion had contact to the subventricular zone, caused widespread oedema, and was highly suggestive of a GB. The left-sided cavernoma which was known since childhood did not change in size throughout the available follow-up. (C–H) Histopathological slides of the tumour specimen from the first and second resections. Retrospective histological and immunohistochemical re-evaluation of the tissue sample from the first surgery revealed an oligodendroglioma, IDH^{mt} and 1p/19q-codeleted (v11b4 brain tumour methylation classifier results, I). The specimen from the second surgery demonstrated an unclassifiable IDH^{wt} glioma with vascular proliferation (J). Scale bar: 50 μ m (C, D, G, H), 20 μ m (E), 100 μ m (F)

TABLE 1 Comparison of tumour tissues

Variant/mutation	Biopsy specimen ^a	First resection	Second resection
<i>IDH1</i> p.(R132H)	✓ (Reads: 36, MAF: 28%)	✓ (Reads: 226, MAF: 46%)	×(wt) (Reads: 602)
<i>TERT</i> c.-124 C > T (C228T)	✓ (Reads: 11, MAF: 27%)	✓ (Reads: 103, MAF: 31%)	✓ (Reads: 149, MAF: 2%)
<i>CIC</i> p.(R215W)	×(wt) (Reads: 19)	✓ (Reads: 229, MAF: 83%)	✓ (Reads: 1037, MAF: 17%)
<i>PIK3CA</i> p.(M1043V)	×(wt) (Reads: 74)	×(wt) (Reads: 402)	✓ (Reads: 1177, MAF: 15%)
<i>TSC1</i> c.2672dup p.N891Kfs*13	✓ (Reads: 68, MAF: 7%)	✓ (Reads: 209, MAF: 39%)	✓ (Reads: 276, MAF: 48%)
1p/19q-codeletion	NA	✓	×
Monosomy chromosome 4	NA	✓	×
<i>CDKN2A/B</i> homozygous deletion	NA	✓	✓
<i>PDGFRA</i> amplification	NA	✓	✓
<i>MGMT</i> promoter methylation	NA	✓	✓
Methylation class (v11b4)	NA	calibrated score 0.99 for “methylation class family Glioma, IDH mutant”, calibrated score 0.99 for the subclass “1p/19q codeleted oligodendroglioma”	calibrated score 0.74 for “methylation class family Glioma, IDH mutant”, calibrated score 0.71 for the subclass “high grade astrocytoma”

Abbreviations: MAF, mutant allele fraction; NA, not available; wt, wild type.

^aOnly low tumour cell content, low overall sequencing quality, methylation analysis not possible.

described [8–11]. Despite the decreasing MAF, the preservation of *CIC* p.R215W may hint at a potential lineage conversion (Table 1). Finally, the acquired methylation class score for the second tumour shows an elevated value for an IDH^{mt} glioma, which may reflect the persistence of various epigenetic alterations of the initially found oligodendroglioma [12].

Moreover, a limited number of tumours with both oligodendroglial and astrocytic characteristics have been reported thus far [13, 14]. An analysis of multicentric low-grade gliomas described patients that demonstrated divergent evolution of IDH^{mt} and 1p/19q-codeleted oligodendroglioma and IDH^{mt} and 1p/19q-intact diffuse astrocytoma, indicating a distinct driver heterogeneity and dual genotype in the very beginning [15]. Despite the “farewell of oligoastrocytoma”, the possibility of solitary tumours harbouring both cell types in the first place seems to remain, especially in the context of selective sampling during biopsy or subtotal resection.

The exceptionally long administration of TMZ, radiation effects and subsequent selection of resistant and initially subclonal IDH^{wt} astrocytic cells could have led to the final malignant glioma. Oligodendrogliomas progressing to oligosarcomas after years of treatment may demonstrate acquired homozygous deletions of *CDKN2A/B*, but usually retain the *IDH1* and *TERT* promoter mutations [5]. The strong decrease of the MAF of *TERT* C228T may indicate a potentially remaining subpopulation of oligodendroglial cells in an overlap region of the first and second tumour. Moreover, oligodendrogliomas usually show better outcomes after RCT and chemotherapy than

astrocytomas, which could have led to complete control of these cells throughout TMZ therapy. TMZ treatment is well known for inducing hypermutation and disabling the MMR pathway, ultimately provoking malignant transformation and chemotherapy resistance [1]. Such transformation could have been exceptionally long delayed herein. The reason, therefore, remains unknown. Moreover, larger panel and exome sequencing would have allowed for the determination of tumour mutational burden. Finally, it is important to note that continuous TMZ administration is not standard of care and is not endorsed by current treatment guidelines.

Besides, the development of the IDH^{wt} glioma could have been independent of the tumour initially diagnosed with imaging given the tumour-inducing effects of the continuous TMZ therapy and previous radiotherapy. Malignant gliomas, IDH^{wt}, with *PDGFRA* amplification, homozygous *CDKN2A/B* deletion, and absence of *TERT* mutation have been reported in secondary gliomas after radiotherapy [4].

Lastly, an independent de novo development of the second tumour without any influence of the applied therapy or based on genetic *TSC1* mosaicism remains possible. Whereas all explanations and hypotheses have their valid arguments, a final explanation cannot be provided. Additional work is needed to further understand gliomagenesis and tumour heterogeneity. This unique case highlights the importance of extended molecular profiling in neuropathology—especially in patients with recurrences and multiple brain tumours—to ensure diagnostic and therapeutic precision and adequate patient care.

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CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

ETHICS STATEMENT AND CONSENT FOR PUBLICATION

The patient provided verbal and written consent for this case report and its publication before death.

AUTHORS' CONTRIBUTIONS

Conceptualization, FE, LS, JR, DK; formal analysis, FE, LS, JR; data curation, FE, AH, JM, EH, LS, JR, DK, writing—original draft preparation, FE, AH; writing—review and editing, FE, AH, JM, EH, MM, JO, SR, AK, LS, JR, DK; visualisation, FE, JM, EH, LS, JR; supervision, LS, JR, DK. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data of this work are not publicly available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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