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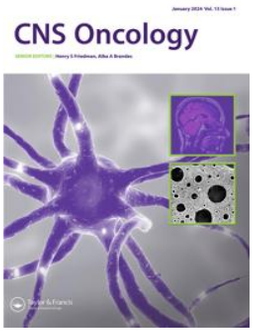

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CASE REPORT

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Synchronous diagnosis of multicentric glioma with distinct isocitrate dehydrogenase molecular profiles: a case report

Aditya A. Mohan[a], Kristen Batich[a,b], Shih-Hsiu J. Wang[b,c], Giselle Y. López[a,b], Michael E. Salacz[d] and Katherine B. Peters[a,c]

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ABSTRACT

This case report characterizes the molecular pathology of two synchronous IDH mutant gliomas in a 28-year-old female patient. The patient exhibited symptoms of dizziness, retro-orbital pain, headache, and numbness with paresthesia in her right arm. MRI imaging revealed two distinct non-enhancing T2/FLAIR hyperintense lesions in the left frontal and parietal lobes. Histopathologic and molecular analyses, including whole exome sequencing, were performed on the resected specimens from each location. The left parietal tumor was diagnosed as a grade 4 astrocytoma with an IDH1 R132H mutation, while the left frontal tumor was classified as a grade 2 oligodendroglioma with an IDH1 R132S mutation. Given the distinct molecular profiles of both synchronous tumors, treatment consideration was given to each individual primary tumor.

PLAIN LANGUAGE SUMMARY

This report describes a young patient with two brain tumors that developed at the same time but in different parts of her brain. Most patients with more than one brain tumor have tumors that are related to each other and come from the same original cancer cell. In this case, each tumor had different genetic features, suggesting they likely formed on their own rather than spreading from one to the other.

Doctors examined both tumors with modern laboratory tests that look at DNA changes. One tumor had changes usually seen in astrocytomas, while the other had changes typical of oligodendrogliomas. These differences helped confirm that the tumors were separate diseases rather than one tumor spreading.

This case shows why it is important to test each tumor individually, rather than assuming they are the same. Understanding the genetics of each tumor can help guide diagnosis, treatment decisions, and future research. Although this situation is rare, it raises new questions about how brain tumors form and why more than one tumor may appear in the same person.

ARTICLE HIGHLIGHTS

- Multicentric gliomas in young adults are rare and require careful diagnostic interpretation.
- In this case, two spatially distinct lesions each carried a different IDH1 hotspot mutation, supporting true biological independence.
- Radiographic evaluation demonstrated no FLAIR continuity or white-matter tract involvement between lesions, supporting a multicentric rather than multifocal process.
- Divergent molecular profiles, including TP53/ATRX loss in one lesion and 1p/19q codeletion with CIC mutation in the other, reinforced distinct lineage assignment.
- The case demonstrates that multicentric gliomas cannot be assumed to share clonal origin and therefore warrant individual histopathologic and molecular characterization.
- Separate profiling of each lesion provided clinically meaningful information for diagnosis, classification, and counseling.
- This report highlights the importance of comprehensive molecular assessment in multicentric glioma presentations to guide accurate diagnosis and future management considerations.
- This case underscores the diagnostic value of integrating imaging, histopathology, and molecular profiling when evaluating patients with synchronous glial neoplasms.

ARTICLE HISTORY

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Multicentric; glioma; IDH1; synchronous; R132H; R132S

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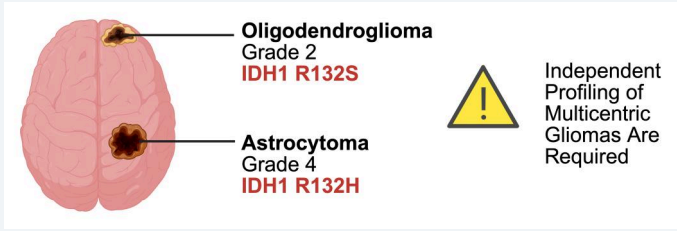
GRAPHICAL ABSTRACT



1. Introduction

Gliomas most often occur as solitary tumors, but on rare occasions, gliomas can be multicentric. It is estimated that the incidence of multicentric glioblastoma, for example, is only 0.5-20% of all malignant gliomas [1]. The occurrence of multiple primary gliomas, defined as distinct and independent tumors originating from different cells or regions within the brain, is an even rarer event. The underlying causes and mechanisms leading to the development of multiple gliomas are still not fully understood, and their diagnosis and management pose significant challenges for clinicians. Molecular characterization offers one potential solution to better understand and characterize multicentric, co-existing, distinct gliomas.

In gliomas, isocitrate dehydrogenase mutations are considered a defining characteristic of a specific subtype, referred to as IDH-mutant gliomas, and are associated with better prognosis compared to IDH-wildtype diffuse gliomas. Given large global differences in molecular and clinical features, the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS) recently reclassified IDH1-mutant glioblastomas as grade 4 IDH-mutant astrocytoma. Mutations in IDH result in neomorphic enzymatic activity, leading to the production of oncometabolite D-2-hydroxyglutarate. Isoforms of IDH are present in the cytoplasm and mitochondria and defined as IDH1 and IDH2, respectively. Within the IDH1 gene, the R132 residue is most frequently mutated. Among low-grade gliomas, the IDH1 R132H, IDH1 R132C, IDH1 R132G, and IDH1 R132S mutations have an incidence of 64.9%, 2.9%, 1%, and 0.5% respectively [2]. Although cases of multiple primary gliomas with different IDH1 mutations have been reported in the context of Li-Fraumeni syndrome [3], to our knowledge this is one of the first reports of primary gliomas with distinct IDH1 mutations occurring independently of Li-Fraumeni syndrome.

Here we describe a case of a patient with a parietal grade 4 astrocytoma bearing an IDH1 R132H mutation and a frontal oligodendroglioma with an R132S mutation.

2. Case report

A 28-year-old right-handed woman presented in July 2020 with a two-month history of loss of balance and bilateral pulsating eye pain, during which she experienced double vision, headache, and numbness and tingling in her right arm. Magnetic resonance imaging (MRI) brain with and without contrast revealed two distinct intra-axial non-contrast enhancing lesions located in separate cerebral regions, one in the left frontal lobe and one in the left superior parietal lobe (Figure 1A). On the transverse plane, the measured center-to-center distance between the two masses was approximately 113 mm, with a minimum edge-to-edge separation of 81.3 mm. The lesions were separated by the displaced left lateral ventricle, with no signal abnormality traversing the white matter between them.

The patient underwent a left parietal craniotomy, awake cortical mapping, and tumor resection. Pathology from resected tissue revealed the left parietal tumor to be astrocytoma, IDH-mutant, CNS WHO grade 4 (IDH1 R132H) based on histology and molecular profiling (Caris Life Sciences). The parietal lesion was resected first because it was the dominant symptomatic focus producing the patient's presenting deficits, consistent with standard neurosurgical practice of addressing the lesion with the greatest immediate clinical impact prior to managing additional tumor sites. Fifteen days later, the patient was readmitted for resection of the left frontal tumor (Figure 1B). Pathology from resected tissue of the left frontal tumor revealed oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 2 (IDH1 R132S, Table 1). Histologic and immunohistochemical analyses are shown (Figure 2). IDH1 R132H immunostaining was positive in the parietal tumor and negative in the frontal tumor; given the mutation specificity of the antibody, the frontal lesion underwent sequencing, which confirmed an IDH1 R132S substitution not detectable by R132H-directed IHC. Immediately after her surgeries, the patient was started on a tapered course of levetiracetam and dexamethasone. After surgery, the patient no longer

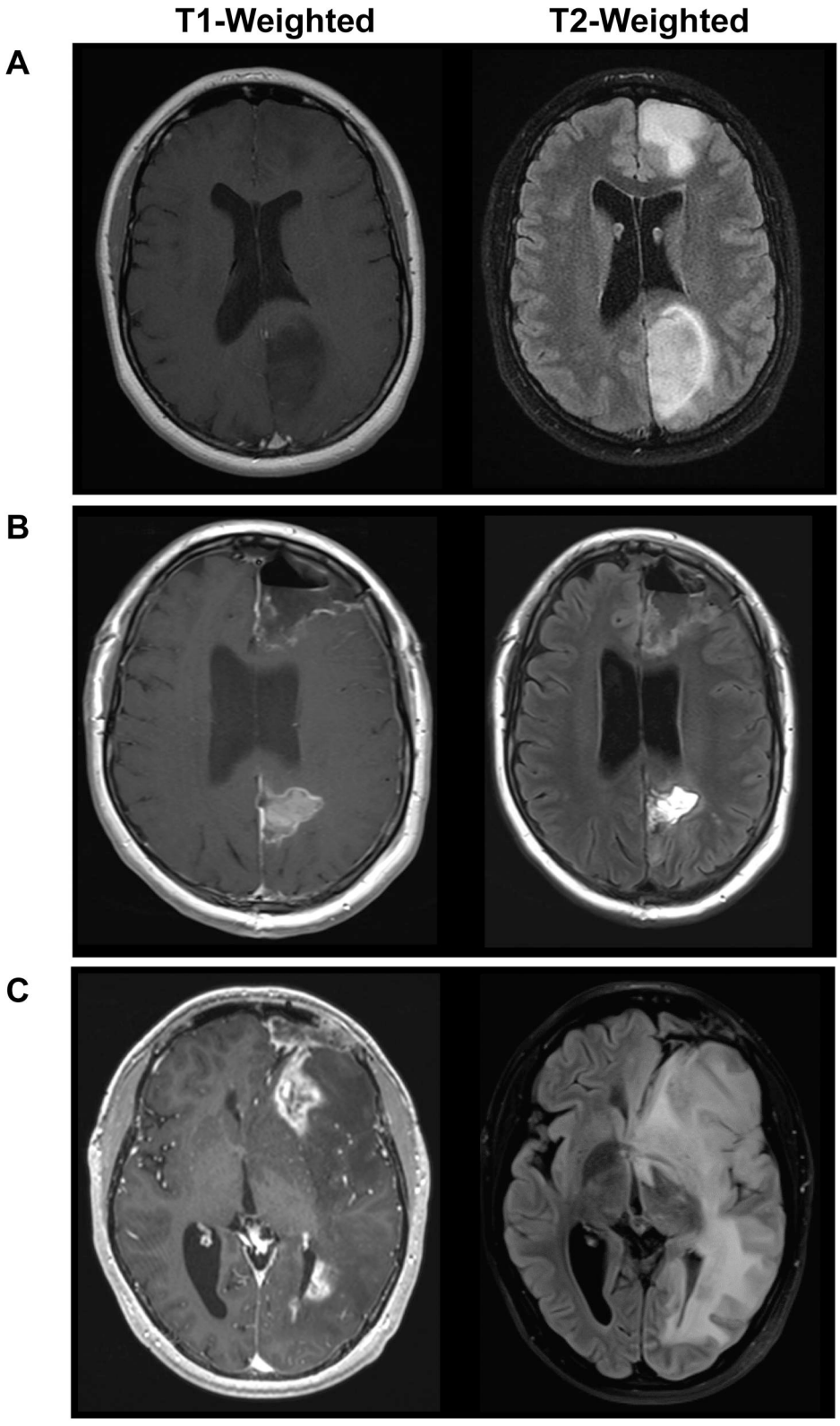


Figure 1. (A) Baseline MRI brain showing two non-enhancing T2 hyperintense lesions in the left frontal and superior parietal lobes. Left: Axial contrast-enhanced T1-weighted sequence. Right: T2-weighted (FLAIR) sequence. (B) Post-operative MRI following resection of the second left frontal tumor. Left: Axial contrast-enhanced T1-weighted sequence. Right: T2-weighted (FLAIR) sequence. (C) MRI brain following six cycles of adjuvant temozolomide. The patient presented acutely with new aphasia and headaches. Left: Axial contrast-enhanced T1-weighted sequence demonstrating increased nodular contrast enhancement in the treated left frontal and left parietal resection cavities. Right: T2-weighted (FLAIR) sequence revealing an expanse in T2 hyperintensity in the left frontal and parietal lobes with corresponding edema and left-to-right midline shift.

Table 1. Integrated clinicopathologic and molecular characterization of synchronous gliomas.

Feature	Left parietal tumor—astrocytoma (IDH-mutant, CNS WHO IV)	Left frontal tumor—oligodendroglioma (IDH-mutant, 1p/19q-codeleted, CNS WHO II)
Histologic diagnosis	Astrocytoma, IDH-mutant, CNS WHO Grade 4	Oligodendroglioma, IDH-mutant, CNS WHO Grade 2
Proliferation index (Ki-67) (IHC)	15%	5–10%
IDH1 mutation (NGS)	R132H with variant allele frequency of 41%	R132S with variant allele frequency of 41%
1p/19q status (copy-number/CNV sequencing)	Intact	Codeleted
ATRX status (IHC)	Loss of nuclear expression	Retained nuclear expression
TP53 status (NGS)	Pathogenic p.Y163C	No pathogenic TP53 alteration detected
CIC status (NGS)	Not detected	Pathogenic p.R202W
TERT promoter status (NGS)	Retained/indeterminate	Pathogenic c.–124C > T
MGMT promoter methylation (pyrosequencing)	Methylated	Methylated
Tumor mutational burden (NGS)	Low (2/Mb)	Low (1/Mb)
Genome-wide loss of heterozygosity (LOH) (NGS)	Low – 4% genomic LOH	Low – 2% genomic LOH
Mismatch repair/MSI status (IHC ± NGS)	MMR-proficient; MSI stable	MMR-proficient; MSI stable
PD-L1 (IHC)	Negative (0%)	Negative (0%)
EGFR status (NGS/CNV)	No mutation/amplification; EGFRvIII not detected	No mutation/amplification; EGFRvIII not detected
Other glioma-associated genes tested but without pathogenic alterations (NGS/CNV)	PTEN, NF1, FUBP1, NTRK1/2/3 fusions, BRAF, PDGFRA, RB1—all negative	PTEN, NF1, FUBP1, NTRK1/2/3 fusions, BRAF, PDGFRA, RB1—all negative

The left parietal lesion harbored a canonical astrocytoma profile defined by *IDH1 R132H*, *TP53* mutation, and *ATRX* loss, whereas the left frontal lesion exhibited a molecularly distinct oligodendroglioma program driven by *IDH1 R132S*, *TERT* promoter mutation, *CIC* alteration, and *1p/19q* codeletion. Shared features included MGMT promoter methylation, MMR proficiency, low tumor mutational burden, and genomically quiet copy-number landscapes. Abbreviations: CNS WHO, Central Nervous System World Health Organization grade; IHC, immunohistochemistry; NGS, next-generation sequencing; CNV, copy-number variation; LOH, loss of heterozygosity; MSI, microsatellite instability; MMR, mismatch repair; PD-L1, programmed death-ligand 1; EGFR, epidermal growth factor receptor.

experienced right arm tingling and numbness but noted changes in taste. One month later, the patient's surgical wounds were found to be infected with *Enterobacter cloacae*, confirmed on culture, and the patient was readmitted for debridement and washout of frontal and parietal wounds. Ten days after debridement, the patient was started on low-dose temozolomide (25 mg twice daily) as bridging therapy while the wound stabilized, in order to minimize the overall interruption in oncologic treatment. One month following washout, the patient initiated standard-of-care radiation therapy (60 Gy in 30 fractions) with concurrent temozolomide (75 mg/m^2) and completed a full course without pauses or delays in treatment. One month following the completion of radiotherapy, the patient began adjuvant five-day temozolomide in 28-day cycles (150 mg/m^2 for cycle 1 and 200 mg/m^2 for remaining cycles) and started tumor-treating fields therapy.

During the sixth cycle of adjuvant temozolomide and tumor-treating fields, the patient was readmitted for aphasia and headaches. MRI brain imaging revealed significant progression consistent with ependymal spread, callosal involvement with significant edema, and nonresectable multifocal disease (Figure 1C). The patient's case was reviewed by multidisciplinary neuro-oncology tumor board, and the patient was started on salvage systemic therapy, which consisted of bevacizumab (10 mg/kg once in 6-week cycle) and lomustine (100 mg/m^2 once in 6-week cycle). After two cycles of the bevacizumab and lomustine regimen, MRI brain imaging revealed a mild increase in the extent of ill-defined enhancement and restricted diffusion in the left periventricular frontal lobe and the left genu of the corpus callosum. Imaging was favored to represent post-therapeutic changes vs. radiation necrosis, although superimposed multifocal tumor progression was not entirely excluded. (Table 2) Cycle 3 of patient's bevacizumab and lomustine course was complicated by thrombocytopenia and anemia. One month later, a close-interval follow-up MRI revealed an increase in amorphous T1 hyperintensity, diffusion restriction, and faint enhancement within the left frontal periventricular-anterior callosal and left periatrial regions. Imaging was again favored to represent post-treatment changes and stable disease. Importantly, the patient described feeling well without any new neurologic symptoms. The patient began cycle 4 with bevacizumab and a 50% dose reduction of lomustine. Unfortunately, the patient passed away unexpectedly from a sudden cardiac arrest.

3. Discussion

Here we describe a unique case of synchronous grade 4 astrocytoma and grade 2 oligodendroglioma, each harboring a distinct IDH1 hotspot mutation. Multicentric gliomas, defined as spatially separated infiltrating gliomas without radiographic continuity, are uncommon, representing approximately 2–5% of diffuse gliomas in sporadic series, with higher rates observed in certain predisposition syndromes [4,5]. Most reported synchronous tumors are multifocal and share key driver mutations, supporting a clonal origin with spread along white-matter tracts or dissemination of early progenitors rather than independent tumorigenic events [6,7]. Against this backdrop, the presence of two anatomically distinct

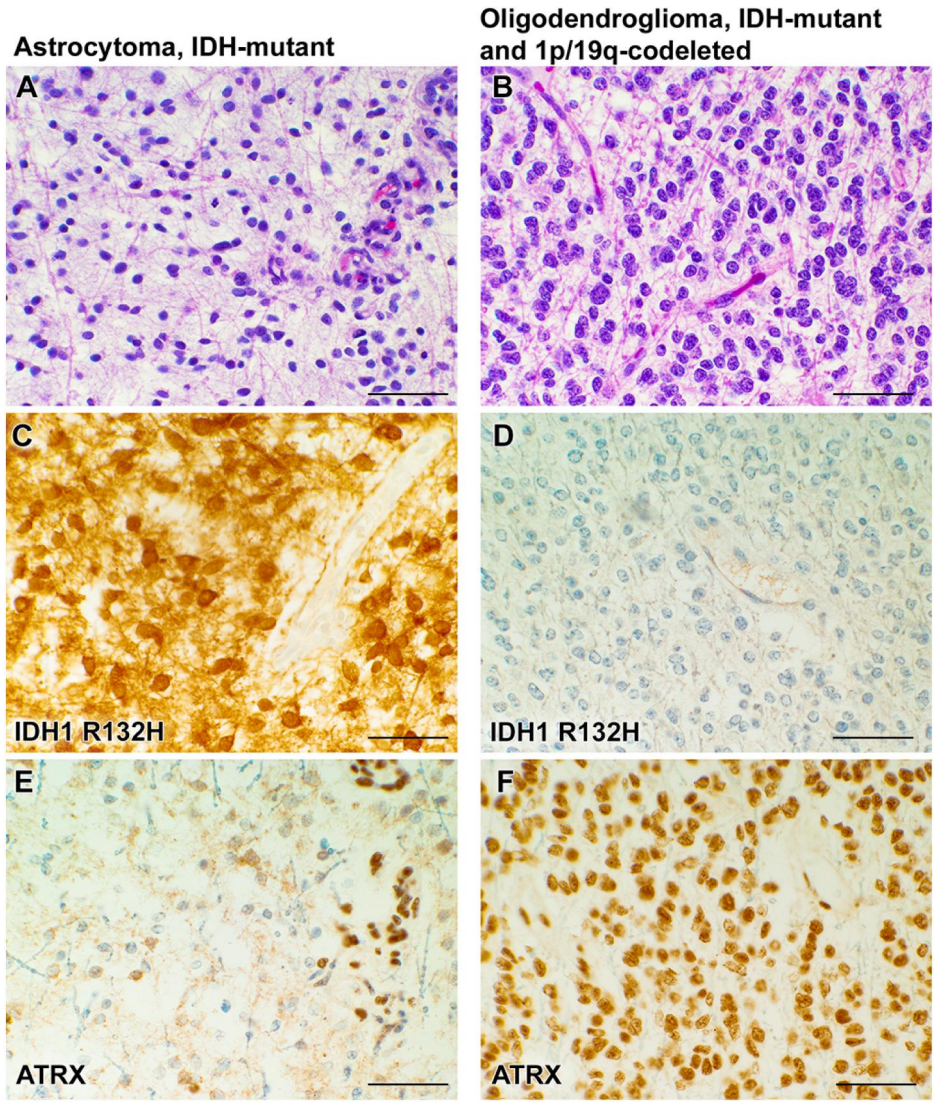


Figure 2. Histologic and immunohistochemical features. (A,C,E) are representative images from the astrocytoma, IDH-mutant, while (B,D,F) are representative images from the oligodendroglioma, IDH-mutant and 1p/19q co-deleted.

Table 2. Lesion-specific postoperative radiographic findings following resection and treatment of synchronous multicentric gliomas.

	Left parietal tumor—astrocytoma (IDH-mutant, CNS WHO IV)	Left frontal tumor—oligodendroglioma (IDH-mutant, 1p/19q-codeleted, CNS WHO II)
Surgical intervention	Left parietal craniotomy with resection of precuneus/superior parietal lesion	Left frontal craniotomy with resection of frontal lesion
Early postoperative imaging	Enhancing resection cavity margins with linear enhancement described as likely at least partly postsurgical; no obvious tumor progression reported at early follow-up	Enhancing resection cavity margins with linear and irregular enhancement; no obvious tumor progression reported at early follow-up
Change in enhancement over time	Linear enhancement described as unchanged on subsequent imaging	Decrease in irregular and linear enhancement on follow-up imaging
Ventricular effects	Early partial effacement of the atrium of the left lateral ventricle; later mild ventriculomegaly described as likely due at least in part to ex vacuo dilatation	Early impression on the frontal horn of the left lateral ventricle; later localized volume loss with ex vacuo dilatation of the left frontal horn
Later Follow Up	Development of focal mass-like enhancement involving the parietal region with associated multifocal ependymal enhancement; report noted possible pseudoprogression or radiation necrosis but considered ependymal enhancement concerning for progression	Development of focal mass-like enhancement; possible pseudoprogression or radiation necrosis but considered enhancement concerning for progression

Table 3. Published examples of synchronous but genetically divergent diffuse gliomas.

Study (year)	Astrocytoma characteristics	Oligodendroglioma characteristics	Reference
Kraus *et al.* (2022)	Left frontal lesion, WHO grade 4, IDH1 wildtype, 1p/19q intact	Right temporal lesion, WHO grade 2, IDH1 R132H mutant, 1p/19q-codeleted	[16]
Singhal *et al.* (2022)	Right frontal lesion, WHO grade 2, IDH1 R132H mutant, ATRX loss, 1p/19q intact	Left parietal lesion, WHO grade 2, IDH1 R132H mutant. 1p/19q-codeleted	[17]
Singhal *et al.* (2022)	Right temporal lesion, WHO grade 2, BRAF V600E mutant, IDH1 wildtype, 1p/19q intact	Left frontal lesion, WHO grade 2, IDH1 mutant, 1p/19q-codeleted	[17]
Nalamada *et al.* (2021)	Right frontal lesion, WHO grade 3, IDH1 mutant, 1p/19q intact	Right frontal lesion, WHO grade 2, IDH1 mutant, 1p/19q co-deleted	[18]

These reports demonstrate anatomical coexistence of astrocytoma and oligodendroglioma with discordant IDH mutation status, 1p/19q codeletion, ATRX expression, or alternative oncogenic drivers (*e.g.*, *BRAF V600E*), emphasizing that separate gliomas can arise independently within the same brain. Our case adds to this body of literature by further illustrating pathway-specific divergence through distinct *IDH1* hotspot variants (*R132H* vs *R132S*).

lesions, each with a different IDH1 hotspot variant (R132H parietal; R132S frontal), is unprecedented in a young adult. Although no additional lesions were identified radiographically or intraoperatively, microscopic disease below MRI detection thresholds cannot be excluded without ultra–high-resolution imaging or postmortem sampling [8].

Very few published reports describe simultaneous astrocytoma and oligodendroglioma (Table 3), and none have documented synchronous lesions with lineage-defining yet biologically divergent IDH1 variants. This pattern argues against dissemination from a common ancestral clone and instead suggests parallel gliomagenesis occurring in separate neural territories. Such a scenario raises important biological considerations: whether a field effect, early epigenetic instability, or divergence within a susceptible progenitor pool allowed two independent tumors to emerge simultaneously. Clinically, these findings reinforce the need to profile each lesion individually, as mutation-specific therapies may differ.

Several mechanisms could explain how two distinct IDH1-mutant gliomas arose in a single patient lacking known hereditary cancer syndromes. One possibility is an underlying predisposition architecture that does not involve classic TP53-driven diseases such as Li-Fraumeni syndrome. Somatic mosaic IDH1/IDH2 mutations, well described in Ollier disease and Maffucci syndrome, demonstrate how post-zygotic alterations can generate a population of at-risk progenitors capable of producing multiple neoplasms, including gliomas [9]. In addition, low-penetrance germline variants such as rs55705857 near CCDC26 substantially increase the risk of IDH-mutant glioma in the general population [10]. Although our patient lacked pathognomonic clinical signs of Ollier disease and Maffucci syndrome such as enchondromatosis and did not undergo germline testing, these data illustrate the possibility of mosaic or inherited susceptibilities which could create a permissive biological landscape for multiple independent IDH-mutant tumors.

Current models of gliomagenesis also support a progenitor-based explanation. Neural stem and oligodendrocyte precursor cells in the subventricular zone and other germinal regions are considered likely cells of origin, and mutations arising within this compartment can seed tumors at anatomically distant sites [11]. Reviews of multicentric glioma highlight that some cases reflect multiple evolutionary trajectories emerging from a genetically abnormal progenitor pool rather than dissemination from a single clone [7]. Within this conceptual framework, separate progenitors in a vulnerable niche could plausibly acquire different IDH1 mutations as early initiating events, producing two spatially distinct but temporally synchronous gliomas. Biochemical differences between IDH1 variants further support the plausibility of divergent evolutionary paths. IDH1 R132 substitutions are not functionally equivalent. They vary in D-2-hydroxyglutarate production and downstream epigenetic remodeling [12,13]. Distinct microenvironmental pressures or lineage contexts may therefore have favored selection of different IDH1 alleles.

This patient underwent treatment before publication of the INDIGO trial and before clinical availability of vorasidenib, so IDH inhibition was neither standard nor feasible at the time. Management was therefore guided by the presence of a grade 4 astrocytoma, leading to use of bevacizumab and lomustine. As mutant-IDH inhibitors such as ivosidenib and vorasidenib enter clinical practice, the specific IDH mutation may increasingly influence therapeutic choices. Although INDIGO included patients with both canonical and noncanonical mutations [14], the clinical significance of subtle biochemical differences remains uncertain, particularly in higher-grade or multicentric disease where efficacy is limited by CNS penetration, tumor burden, and timing of therapy. Not all IDH1 variants exhibit equivalent pharmacologic profiles: for example, while the IC_{50} of ivosidenib is 12 nM for IDH1

R132H and IDH1 R132S, it is 13 nM and 8 nM for IDH1 R132C and IDH1 R132G, respectively [15]. Similarly, in the case of vorasidenib, the IC_{50} for IDH1 R132H and IDH1 R132S is 6 nM while the IC_{50} for IDH1 R132C and IDH1 R132G is 19 nM and 17 nM respectively [15]. Although IC50 estimates suggest differential susceptibility of the R132H- and R132S-mutant IDH1 proteins to ivosidenib and vorasidenib, the clinical significance of these values remains uncertain. Currently, the IC50 data differences between IDH1 mutations are insufficient to inform off-label therapeutic use and while the pharmacologic data are mechanistically intriguing, they highlight a larger unmet need for further studies to advance mutation-guided application of IDH inhibitors.

As summarized in Table 1, neither tumor's molecular profile strongly suggested a hereditary syndrome. Both were mismatch repair–proficient, microsatellite stable, and genomically quiet, consistent with canonical sporadic IDH-mutant gliomas. In the absence of hypermutation, syndromic features, or compelling family history, broad germline evaluation was not pursued. Nonetheless, contemporary neuro-oncology increasingly recommends germline testing in young patients with multicentric gliomas, making its omission a limitation. This case's interpretive power is inherently limited by its single-patient nature. Although the distinct IDH1 mutations strongly support biological independence of the lesions, the absence of matched germline sequencing and comprehensive clonality analyses prevents definitive proof. Radiologic classification as multicentric cannot exclude microscopic connections below MRI resolution. The tumor microenvironment, epigenetic state, and potential field effects remain speculative without experimental interrogation. Given the rarity of two spatially distinct gliomas with different IDH1 mutations, additional susceptibility testing would have been valuable.

In conclusion, managing patients with multiple gliomas harboring distinct IDH1 mutations requires an individualized strategy that integrates histology, molecular subtype, and patient-specific genetic risk. Advances in targeted therapy and genomic profiling are improving our ability to tailor treatment, and future research will be essential to understanding how specific IDH1 variants shape tumor behavior and therapeutic response [16–18].

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Author contributions

KB and KP contributed to conceptualization; AM and KB to data curation, formal analysis, and validation; KB, KP, SW, GS, MS, and GL to investigation and resources; KP to supervision and project administration; AM to visualization; and AM, KB, and KP to writing – original draft, with all authors contributing to writing – review and editing.

Ethical declaration

The authors adhered to the CARE guidelines in writing this case report. This case report did not require approval from an institutional ethics committee per institutional guidelines, as it describes a single patient and involves no experimental intervention beyond standard clinical care. Written informed consent for publication of deidentified data and images was obtained directly from the patient. This study was conducted in accordance with the Declaration of Helsinki.

Disclosure statement

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.

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