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CASE REPORT

Ganglioglioma with *MAP2K1* Mutation and *CDKN2A/B* Homozygous Deletion: A Case Report

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Abstract

Aims/Background Gangliogliomas are grade 1 glioneuronal tumors occurring predominantly in the temporal lobe, as per the World Health Organization (WHO) classification. Gangliogliomas often harbor *BRAF* (v-Raf murine sarcoma viral oncogene homolog B1) p.V600E hotspot mutation or other alterations leading to activation of RAS/RAF/MAPK (rat sarcoma virus oncogene/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase) signaling pathway, which is the driver factor of this tumor. This study aims to investigate a case of ganglioglioma patient with distinctive molecular features, and to present the clinical and pathological characteristics as well as the treatment employed for this individual.

Case Presentation We reported a primary ganglioglioma harboring *MAP2K1* (mitogen-activated protein kinase kinase 1) mutation and *CDKN2A/B* (cyclin-dependent kinase inhibitor 2A/2B) homozygous deletion in a 4-year-old patient. The patient experienced tumor recurrence 12 months after gross total resection of the tumor. Subsequently, salvage chemotherapy with a combination of temozolomide and irinotecan was administered, resulting in effective control of the tumor.

Conclusion To our knowledge, this is the first reported case of ganglioglioma with anaplastic features harboring *MAP2K1* mutation and homozygous deletion of *CDKN2A/B*. These findings may shed light on the genetic features of ganglioglioma and offers insights into potential therapeutic approaches for this rare neoplasm.

Key words: ganglioglioma; *MAP2K1* mutation; *CDKN2A/B* homozygous deletion; anaplastic; chemotherapy

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Introduction

Gangliogliomas are rare grade 1 glioneuronal tumors, according to the World Health Organization (WHO) classification, with an annual incidence rate of 0.186 cases per 100,000 population (Darlix et al, 2017). Gangliogliomas often affect children and adolescents, who are commonly diagnosed at the median age of 12 years. Most gangliogliomas occur in the temporal lobe and patients with this medical condition are often accompanied by a history of focal seizures (Prayson et al, 1995; Wolf et al, 1994). Gangliogliomas are composed of two distinct components: neuronal and glial elements, which are either mixed or separated. The activation of RAS/RAF/MAPK (rat sarcoma virus oncogene/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase) signaling pathway is the main driver

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of ganglioglioma pathogenesis. Approximately 10–60% of these tumors harbor *BRAF* (v-Raf murine sarcoma viral oncogene homolog B1) p.V600E hotspot mutation (WHO Classification of Tumours Editorial Board, 2021). Gangliogliomas have a good prognosis, and most patients can achieve long-term survival after gross total resection (Compton et al, 2012; Luyken et al, 2004; Yust-Katz et al, 2014). However, certain tumors may have anaplastic characteristics, such as prominent mitotic activity and high Ki-67 index. In addition, patients with rare gangliogliomas carrying both *BRAF* p.V600E mutation and *CDKN2A* (cyclin-dependent kinase inhibitor 2A) homozygous deletion were reported to have a poor prognosis (Pekmezci et al, 2018a).

MAP2K1 (mitogen-activated protein kinase kinase 1, MEK1) is a dual-specific serine/threonine and tyrosine kinase, which plays an important role in activating and regulating the RAS/RAF/MAPK signaling pathway. When phosphorylated by RAF kinases, MAP2K1 phosphorylates and activates the downstream signal ERK1/2 (extracellular signal-regulated-kinase 1/2) (Chen et al, 1996). *MAP2K1* mutations are common in a variety of malignant tumors, including lung adenocarcinoma, ovarian cancer and melanoma (Drosten et al, 2014; Gershenson et al, 2022; Hodis et al, 2012), whereas *MAP2K1/MAP2K2* mutations are rare in gangliogliomas. It has been reported that the pathological patterns of a recurrent anaplastic glioneuronal tumor harboring a *MAP2K1* mutation and homozygous deletion of *CDKN2A/B* (cyclin-dependent kinase inhibitor 2A/2B), with its primary tumor diagnosed as ganglioneuroma, were difficult to determine (Cheaney et al, 2019).

Here, we report a case of primary ganglioglioma harboring *MAP2K1* mutation and *CDKN2A/B* homozygous deletion, offering valuable insights into the molecular pathogenesis of gangliogliomas.

Case Presentation

Patient Characteristics and Operation

This case presents a 4-year-old girl who had suffered from a one-month history of attention loss and lip cyanosis in July 2021. Computed tomography (CT) scan demonstrated a left temporal lobe occupation with mild calcification (Fig. 1A,B). However, magnetic resonance imaging (MRI) was not been performed at the same time. In August 2021, the patient underwent gross total resection of the tumor at a local hospital. She remained neurologically asymptomatic and did not experience seizures postoperatively.

Histopathologic Examination

The hematoxylin and eosin (HE) staining demonstrated two distinct morphological patterns. The cell-dense regions consisted of spindle-shaped cells with oval or elongated nuclei and granular chromatin. Certain tumor cells showed slender processes. Other regions were characterized with lower cellularity with enlarged dysmorphic neuron or ganglion cells and scattered calcification (Fig. 2A,B). We found 2–3 mitoses on each 10× high-power fields. With immunohistochemical staining, the tumor cells were found to be positive for oligodendrocyte transcription

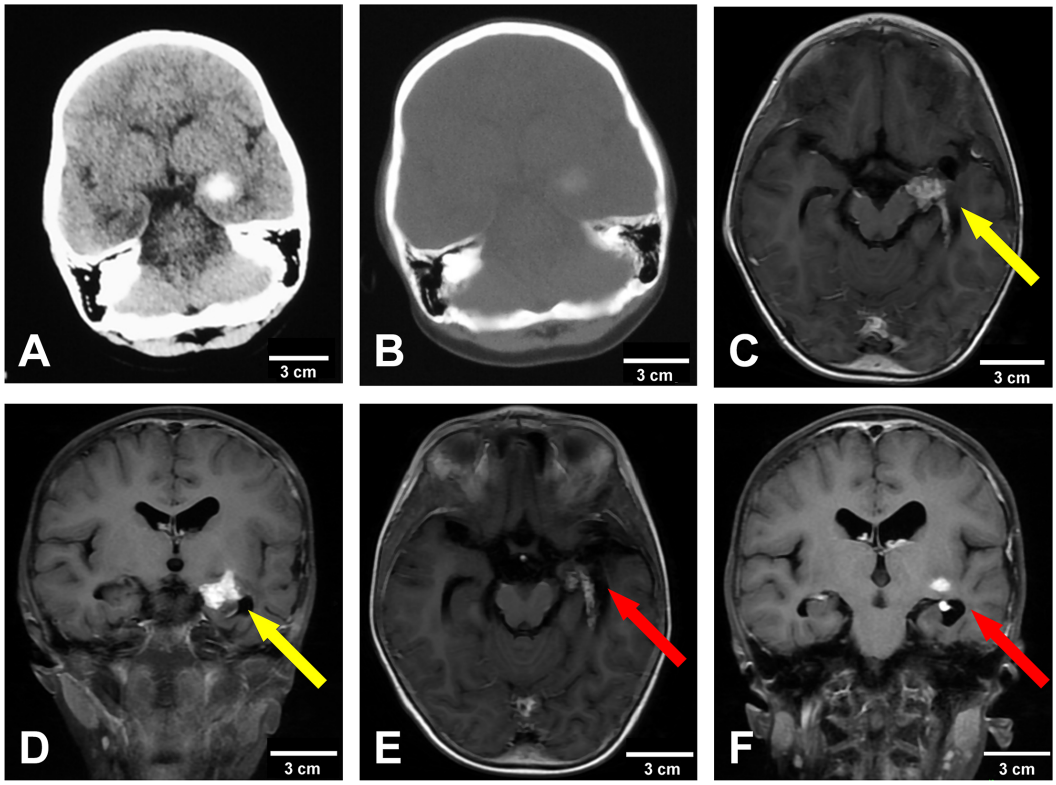

Fig. 1. Radiographic images of the tumor. (A,B) Preoperative computed tomography (CT) scan demonstrated a left temporal lobe occupation with mild calcification. (C,D) Twelve months after operation, the magnetic resonance imaging (MRI) scan revealed a medial temporal lobe mass (17 × 14 mm) with heterogeneous contrast enhancement (yellow arrows). (E,F) After 9 cycles of temozolomide and irinotecan treatment, the tumor shrank in size (red arrows). The scale bars represent 3 cm.

factor 2 (Olig-2), glial fibrillary acidic protein (GFAP), microtubule-associated protein 2 (MAP2), and synaptophysin (Syn) expression (Fig. 2C–F), whereas chromogranin A (CgA)-positive cells was occasionally interspersed in the tumor (Fig. 2G). Besides that, neuronal nuclei (NeuN) expression was occasionally found in background neoplastic neuron-like cells. CD34 staining was positive only in a minority of cells or small vessels (Fig. 2H). IDH1 (isochlorate dehydrogenase 1) and BRAF staining were negative, and the Ki-67 index measured about 10% in hotspot area (Fig. 2I). According to these histopathologic findings, the tumor was consistently characteristic of ganglioglioma, with a WHO classification grade of 2 to 3.

Molecular Pathology

Genetic testing was performed by Simcere Diagnostics, Nanjing, China, using a previously described methodology (Wang et al, 2023). A *MAP2K1* mutation (L98_I103del) within exon 3 was identified by next-generation sequencing, and the frequency of its mutant allele was 25.64%. The tumor also harbored a deletion on sequence 9p22.1 to 9p21.2 that contains tumor suppressor genes *CDKN2A* and *CDKN2B* (Fig. 3A,B). By utilizing fluorescence *in situ* hybridization (FISH), we identified that the deletion of *CDKN2A* and *CDKN2B* was homozygous in nature (Fig. 3C). Mutations activating the RAS/RAF/MAPK signaling pathway, such

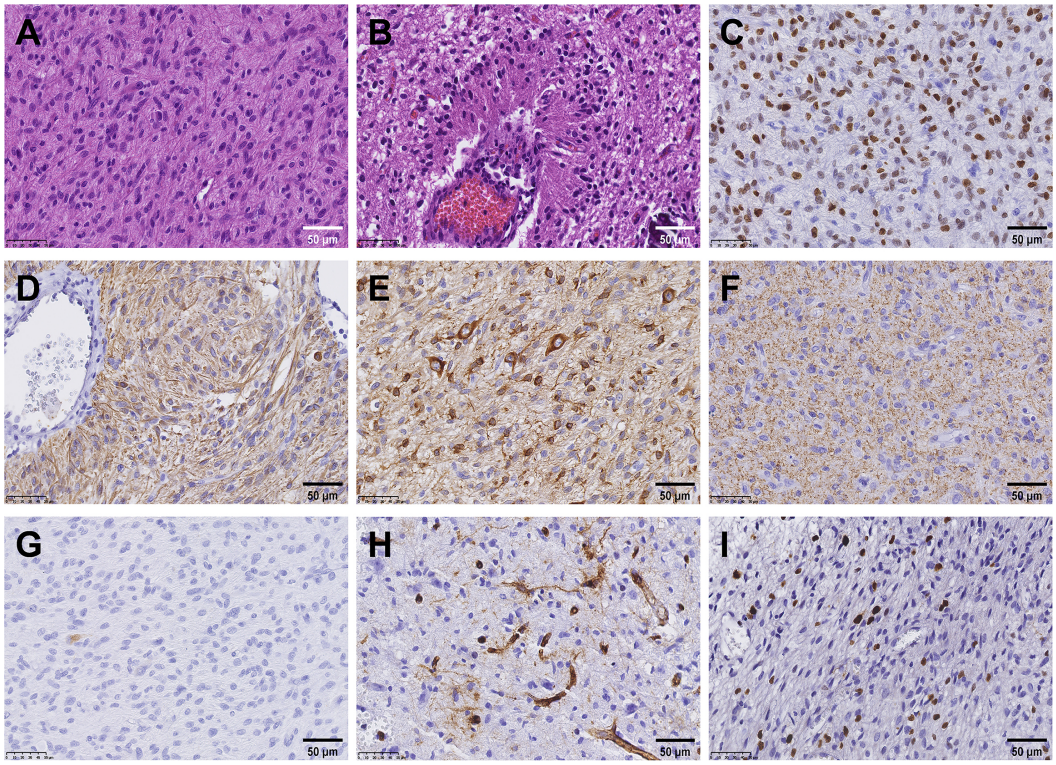

Fig. 2. Histologic features of the tumor. (A,B) The tumor demonstrated two distinct morphological patterns. The cell-dense regions consisted of spindle-shaped cells with oval or elongated nuclei and granular chromatin. Other regions were characterized with lower cellularity with scattered calcification (HE (hematoxylin and eosin) staining, 400× magnification). (C–F) Positive immunohistochemical staining of oligodendrocyte transcription factor 2 (Olig-2) (C), glial fibrillary acidic protein (GFAP) (D), microtubule-associated protein 2 (MAP2) (E) and synaptophysin (Syn) (F) (400× magnification). (G) Occasional detection of chromogranin A (CgA)-positive cells (400× magnification). (H) Detection of positive CD34 staining only in a minority of cells or small vessels (400× magnification). (I) Ki-67 index of about 10% estimated based on the staining outcomes in hotspot area (400× magnification).

as *BRAF* mutation, *BRAF* gene fusions, *NF1* (neurofibromin 1) mutation, *KRAS* (Kirsten rat sarcoma viral oncogene homolog) mutation and *FGFR1/2/3* (fibroblast growth factor receptor1/2/3) mutation, were not identified in this case, and the typical genetic alterations in other high-grade gliomas, including those in *IDH1/2*, *TERT* (telomerase reverse transcriptase), *H3-K27M* (Histone 3 lysine27-to-methion ine), *ATRX* (alpha thalassemia/mental retardation syndrome X-linked), *TP53* (tumor protein p53), *EGFR* (epidermal growth factor receptor), *RELA* (reticuloendotheliosis oncogene homolog A), *YAP1* (Yes1 associated transcriptional regulator) or *MYB* (myeloblastosis oncogene), were not detected. No copy number alterations such as chromosome 1p loss, 19q loss, 10 loss or 7 gain was identified. O6-methylguanine-DNA methyltransferase (MGMT) promoter was unmethylated (0.06%). The tumor had a stable microsatellite profile, with the proportion of programmed cell death-ligand 1 (PD-L1)-positive cells of less than 1%.

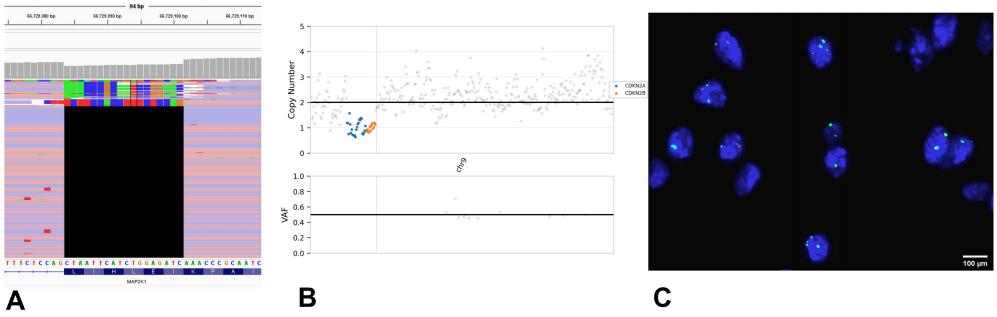

Fig. 3. Molecular and genetic features of this tumor. (A) Next-generation sequencing revealed a *MAP2K1* (mitogen-activated protein kinase kinase 1) mutation (L98_I103del) within exon 3. (B) The tumor also harbored a deletion on the sequence 9p22.1 to 9p21.2 that contains tumor suppressor genes *CDKN2A* (cyclin-dependent kinase inhibitor 2A) and *CDKN2B* (cyclin-dependent kinase inhibitor 2B). (C) The homozygous deletion of *CDKN2A* and *CDKN2B* was identified by fluorescence *in situ* hybridization (FISH). The *CDKN2A* is stained red while the centromere is dyed green (original magnification, 100×).

Treatment and Outcome

The patient received one cycle of chemotherapy (cisplatin, etoposide and vincristine) postoperatively. Subsequently, she received a 6-week focal radiation treatment (60 Gy/30 f) in combination with temozolomide (on days 1–42), irinotecan (on days 1–3) and vindesin (on day 1), followed by 6 cycles of chemotherapy (cisplatin, etoposide and ifosfamide) in a local institution.

In July 2022, the MRI scan revealed a medial temporal lobe mass (17 × 14 mm) with heterogeneous contrast enhancement, indicating tumor recurrence *in situ* (Fig. 1C,D). Given the patient's young age and the relatively brief interval between tumor recurrence and the first operation, chemotherapy was deemed the preferred approach. The patient received 9 four-weekly cycles of temozolomide (150 mg/m^2, on days 1–5) and irinotecan (150 mg/m^2, on day 1 and day 14). The major adverse events occurring during the treatment included grade 3 leukopenia and grade 4 elevated aminotransferase. At the end of the treatment, the volume of tumor was reduced (Fig. 1E,F). At the time of writing this report, the patient remained asymptomatic and was capable of engaging in normal daily activities.

Discussion

Here we described a case of ganglioglioma with anaplastic features that harbored both *MAP2K1* mutation and *CDKN2A/B* homozygous deletion. Generally, the growth of gangliogliomas is driven by activation of MAPK signaling pathway, which is induced by the most common mutation *BRAF* p.V600E and other genetic alterations including in-frame insertion of *BRAF* p.R506, *BRAF* fusion, *RAF1* gene fusion, *KRAS* mutation, and *NF1* mutation (Pekmezci et al, 2018a). The tumor we reported did not carry the above-mentioned mutations, except for *MAP2K1* mutation, which can lead to increased phosphorylation levels of MEK and ERK, thereby activating the MAPK signaling pathway. Conversely, a previous study on 40 typi-

cal gangliogliomas revealed that no mutations in *MAP2K1* were detected (Pekmezci et al, 2018a).

In glial neuronal tumors, *MAP2K1* mutations are frequently observed in multinodular and vacuolating neuronal tumors (MVNTs), which are classified as WHO grade 1 tumors and exhibit nodular morphological changes characterized by monom orphic neuronal components. The volume of MVNTs cell is slightly smaller than that of ganglion cells, and the cells feature round and vesicular nuclei, prominent nucleoli, and amphophilic to eosinophilic cytoplasm (Huse et al, 2013; Nagaishi et al, 2015; Thom et al, 2018). Notably, some tumors have been reported to contain mixed MVNTs and ganglioglioma-like components (Pekmezci et al, 2018b; Thom et al, 2018), which is suggestive of a close association between MVNTs and gangliogliomas. However, the pathological features of this tumor did not align with those typically seen in MVNTs.

CDKN2A/B homozygous deletion is frequently observed in various central nervous system tumors, including IDH-mutant astrocytoma, meningioma, and ependymoma (Korshunov et al, 2010; Louis et al, 2021), and it is associated with a poor prognosis. The incidence of homozygous deletion of *CDKN2A/B* in ganglioglioma is relatively low, with only 3 out of 40 cases harboring homozygous deletion of *CDKN2A*. This rare incident may potentially have an increased risk of recurrence (Lassaletta et al, 2017; Pekmezci et al, 2018a). Although the prognostic significance of homozygous deletion of *CDKN2A* in ganglioglioma remains uncertain, this particular case demonstrates the potential link of the deletion with anaplastic features and rapid postoperative recurrence, suggesting an unfavorable prognosis for those carrying such genetic mutation.

Cheaney et al (2019) reported a tumor harboring both *MAP2K1* mutation and *CDKN2A/B* homozygous deletion, which included regions exhibiting low-grade and high-grade morphological features. The region with low-grade morphological features displayed characteristics consistent with MVNT, while the other region fit into the category of ganglioglioma. Both regions harbored homozygous deletions of *MAP2K1* and *CDKN2A/B*, indicating distinct morphologies within the same monoclonal tumor (Cheaney et al, 2019). However, our case did not exhibit pathological features associated with MVNT.

Recent research has demonstrated that some gangliogliomas exhibiting high-grade or anaplastic features acquired homozygous deletion of *CDKN2A/B* at recurrence (Vizcaino et al, 2024). Considering the extended disease course lasting up to 30 years in the patient reported by Cheaney et al (2019), it is plausible for this tumor to acquire the aforementioned genetic alterations during relapse. Specifically, the current case focused on a primary tumor and proposed that *MAP2K1* mutation and *CDKN2A/B* homozygous deletion represent early events in tumorigenesis, potentially precipitating the anaplastic features and rapid recurrence of this tumor. These findings and postulation provide valuable insights into the genetic component of gangliogliomas. Further investigation is warranted to elucidate the prevalence of *MAP2K1* mutation in ganglioglioma and its prognostic implications.

There is a relatively limited range of treatment options available for anaplastic or recurrent gangliogliomas, and adding to this treatment challenge is the lack

of standard therapeutic regimen. Considering the anaplastic feature of this tumor, we treated it with temozolomide and irinotecan. Temozolomide is extensively utilized in the treatment of high-grade gliomas, particularly in tumors with *MGMT* promoter methylation (Hegi et al, 2005; Weller et al, 2017). Irinotecan, when used in combination with drugs such as bevacizumab, is effective against glioblastomas and medulloblastomas (Levy et al, 2021; Mesti et al, 2015). However, research data on its efficacy for gangliogliomas remain limited, especially for those displaying high-grade features similar to the case mentioned above. In this case, the tumor shrank in response to the combined treatment of temozolomide and irinotecan, suggesting that further investigation into this regimen is warranted. Additionally, previous study has demonstrated that combining BRAF inhibitor dabrafenib with MEK inhibitor trametinib has a therapeutic effect on pediatric low-grade gliomas harboring *BRAF* p.V600E mutations (Bouffet et al, 2023). In the current case, the tumor harbored a *MAP2K1* mutation (L98_I103del), which may activate signaling pathways through constitutive kinase activity independent of RAF and does not co-occur with *RAF*, *RAS* or *NF1* mutations as shown by a previous study (Gao et al, 2018). Tumors carrying such mutations may exhibit poor responsiveness to RAF or MEK inhibitors, highlighting the need for further investigations into novel selective MEK inhibitors tailored to these specific tumor types.

Conclusion

In summary, we present the first reported case of ganglioglioma with anaplastic features harboring *MAP2K1* mutation and homozygous deletion of *CDKN2A/B*, laying a concrete foundation for further exploration of the genetic components of gangliogliomas and offering insights into potential therapeutic approaches for this rare neoplasm.

Learning Points

- *MAP2K1* mutation in ganglioglioma may result in activation of the RAS/RAF/MAPK signaling pathway.
- Homozygous deletion of *CDKN2A/B* may be associated with the anaplastic features and poor prognosis in a minority of gangliogliomas.
- Conventional chemotherapy agents, such as temozolomide and irinotecan, have shown efficacy for treating gangliogliomas with anaplastic features; however, further research is warranted to validate their effectiveness.
- Identifying molecular features is crucial for paving way for development of targeted therapies for recurrent/anaplastic gangliogliomas.

Availability of Data and Materials

The data used to support the findings of this study are available from the corresponding author upon request.

Author Contributions

JZ designed the study. CZ and CL acquired the data. CZ, CL and JG analyzed the data. CZ drafted the article. JZ and JG critically revised the article. JZ reviewed the submitted version of manuscript. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All procedures performed in this study 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. The study was reviewed and approved by the human subjects' institutional review boards of Sanbo Brain Hospital of Capital Medical University (Ethical approval number: SBNK-YJ-2024-024-01). Written informed consent was obtained from the patient's family.

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Conflict of Interest

The authors declare no conflict of interest.

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