doi: 10.2176/jns-nmc.2024-0269

NMC Case Report Journal 12, 139-146, 2025

Favorable Response to Conventional Chemoradiotherapy in Radiation-induced Glioma Harboring Coamplification of PDGFRA, KIT, and KDR: A Case Report and Literature Review

Daisuke TANIKAWA,[1] Mitsuaki SHIRAHATA,[1] Kokyo SAKURADA,[1] Masayoshi FUKUOKA,[1] Reina MIZUNO,[1] Ayaka SAKAKIBARA,[2] Masayo KANEKO-MISHIMA,[1] Takuro EHARA,[1] Tatsuya OZAWA,[1] Tomonari SUZUKI,[1] Taku HOMMA,[3] Shingo KATO,[4] and Kazuhiko MISHIMA[1]

[1]*Department of Neurosurgery/Neuro-oncology, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan*
[2]*Department of Breast Oncology, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan*
[3]*Department of Diagnostic Pathology, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan*
[4]*Department of Radiation Oncology, Saitama Medical University International Medical Center, Hidaka, Saitama, Japan*

Abstract

One of the most serious complications of cranial radiotherapy is the development of radiation-induced glioma, which is estimated to occur in 1%-4% of patients who have received cranial irradiation and has a worse prognosis than sporadic glioblastoma. Although comprehensive genetic analysis has recently uncovered the molecular characteristics of radiation-induced glioma, the full picture remains unclear due to its rarity. A 45-year-old man presented with generalized seizures caused by multiple brain tumors involving the right frontal lobe, thalamus, and brainstem. The patient had a history of whole-brain radiotherapy for recurrent Burkitt's lymphoma at the age of 12. He underwent craniotomy, and the histological diagnosis revealed a high-grade glioma with isocitrate dehydrogenase-wildtype, which was presumed to be a radiation-induced glioma that developed 33 years after whole-brain irradiation. Next-generation sequencing identified a *CDKN2A/B* deletion, as well as coamplification of several receptor tyrosine kinases-encoding genes, including *PDGFRA*, *KIT*, and *KDR*, all of which are located at 4q12. Amplification of this region is broadly observed across cancers and is associated with poor prognosis in sporadic glioblastoma. Nevertheless, the patient received chemoradiotherapy with temozolomide, followed by temozolomide maintenance therapy, resulting in a complete response of all lesions. Although radiation-induced gliomas are generally difficult to treat, our patient unexpectedly responded well to conventional chemoradiotherapy despite the coamplification of multiple receptor tyrosine kinases-encoding genes, which is typically suggestive of an aggressive phenotype. Our case indicates that some radiation-induced gliomas may have distinct molecular characteristics influencing the therapeutic response, which differ from those of sporadic glioblastomas.

Keywords: radiotherapy, radiation-induced glioma, 4q12 amplification, next-generation sequencing

Introduction

Cranial radiotherapy (RT) plays an important role in the treatment of various brain tumors and was previously used as prophylactic therapy for the central nervous system (CNS) in pediatric acute lymphoblastic leukemia (ALL), but it also carries long-term risks. One of the most serious delayed risks is the development of radiation-induced glioma

Received October 28, 2024; Accepted December 27, 2024

(RIG). According to the National Cancer Institute's Surveillance, epidemiology, and End Results program, the incidence of RIG is estimated to be 1%-4% in patients who have received cranial irradiation. RIG accounts for 2%-10% of deaths in patients with pediatric brain tumors.[1] The risk of developing RIG increases with the cumulative time since RT was administered. A study of 371 patients who received cranial irradiation during childhood revealed an incidence of 1.60% at 10 years and 3.02% at 15 years.[2] The primary malignancies in patients with RIG were predominantly ALL and various brain tumors, with common radiation doses ranging from 21 to 30 Gy for ALL and 41 to 60 Gy for brain tumors.[3] The Childhood Cancer Survivor study demonstrated that the risk of developing RIG increased with radiation doses above 10 Gy, with the highest risk observed in the 30-45 Gy range.[4] The median latency period from RT development was approximately 9 years (range: 2.5-61 years).[3,4]

The rarity of RIG makes it difficult to conduct clinical trials, and no standard of care for RIG has been established to date. Based on retrospective data, re-irradiation is considered effective, albeit with dose limitations.[3] The prognosis for patients with RIG is poor, with a median survival of less than 1 year—worse than that of patients with sporadic glioblastoma (GBM).[1,3,5,6] This may be due to differences in the underlying molecular properties between RIG and sporadic GBM, as well as dose limitations in RT due to prior irradiation. Although recent studies have comprehensively characterized the molecular biology of RIG using next-generation sequencing (NGS) and deoxyribonucleic acid (DNA) methylation profiling,[2,5-8] the molecular characteristics of RIG remain incompletely understood.

The *PDGFRA*, *KIT*, and *KDR* genes encoding receptor tyrosine kinases (RTKs) are all located on chromosome 4q12, and amplification of this region is broadly present across cancers, with particularly marked enrichment in sporadic GBMs, indicating worse outcomes.[9,10] Here, we report a case of RIG with *CDKN2A/B* deletion as well as coamplification of *PDGFRA*, *KIT*, and *KDR*, in which combined RT and temozolomide (TMZ) resulted in a complete response—an exceptional outcome in patients with sporadic GBM.

Case Report

A 45-year-old man presented with generalized seizures. Magnetic resonance imaging (MRI) showed multiple gadolinium-enhancing lesions in the right frontal lobe and non-enhancing lesions with hyperintensity on fluid-attenuated inversion recovery (FLAIR) involving the right thalamus and right midbrain (Fig. 1a-c). The patient had a treatment history of Burkitt's lymphoma of the ileal region at the age of 10, receiving chemotherapy with vincristine, prednisolone, doxorubicin, cyclophosphamide, and methotrexate, and a CNS relapse at the age of 12, for which he had received 24 Gy of whole-brain irradiation and 12 Gy of whole-spine irradiation. He underwent partial resection of the right frontal lobe tumor, and the pathology showed diffuse infiltrative proliferation of atypical cells with dense chromatin staining and poor cytoplasm, with abundant capillaries, and multinucleated cells observed in some areas. Neither necrosis nor microvascular proliferation was observed (Fig. 2a). Immunohistochemically, the neoplasm did not express any lymphocytic markers, such as CD20, CD79a, CD3, CD5, PAX5, and TdT. On the other hand, the neoplastic cells were focally immunopositive for glial fibrillary acidic protein (GFAP) (Fig. 2b), and diffusely immunopositive for oligodendrocyte transcription factor 2 (OLIG2) and SOX10 (Fig. 2c and d). No isocitrate dehydrogenase 1 (IDH1) R132H expression was observed (Fig. 2e), and nuclear expression of alpha-thalassemia/mental retardation syndrome X-linked (ATRX) protein was observed (Fig. 2f). Weak p53 nuclear expression was observed in scattered neoplastic cells (Fig. 2g). The Ki-67 labeling index was around 70% (Fig. 2h). Those histopathological and immunohistochemical findings led to the diagnosis of high-grade glioma, consistent with an RIG that developed 33 years after whole-brain irradiation based on Cahan's criteria.[11] Genetically, *IDH1/2*-wildtype was confirmed by Sanger sequencing. The methylation-specific polymerase chain reaction showed that the O6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter was unmethylated. NGS analysis identified *CDKN2A/B* deletion as well as coamplification of several RTK-encoding genes, including *PDGFRA*, *KIT*, *KDR*, *MET*, and *EPHB4*. Immunohistochemistry confirmed the NGS results. Tumor cells were diffusely immunopositive for PDGFRA (Fig. 2i) and c-MET (Fig. 2j), with lost MTAP expression (Fig. 2k). Microsatellite instability status was assessed as stable, and tumor mutational burden was 6 per megabase. The Heidelberg DNA-methylation brain_classifier_v12.8 classified this case as diffuse pediatric-type high-grade glioma, RTK1 subtype, subclass C, with a calibrated score of 0.6029.[12] Copy-number profile derived from DNA methylation array data showed copy-number alterations (CNAs) characteristic of RIGs, such as *CDKN2A/B* homozygous deletion and *PDGFRA* amplification, as well as *MET* amplification with marked CNAs across the genome, aligning with NGS results (Fig. 2l). Postoperatively, 11C-methionine positron emission tomography (PET) showed strong uptake in the residual right frontal lobe tumor (Fig. 1d). He received conventional chemoradiotherapy (CRT) with TMZ. Considering the history of whole-brain irradiation, RT was administered with 50 Gy in 25 fractions to the right frontal lobe lesion and 36 Gy in 18 fractions to the right thalamus and midbrain lesions. Maintenance chemotherapy with monthly TMZ was started after a 4-week break following the completion of CRT, and MRI after 3 courses of TMZ showed a complete response in all lesions (Fig. 1e and f). Subsequently, a total of 12 courses of TMZ maintenance therapy

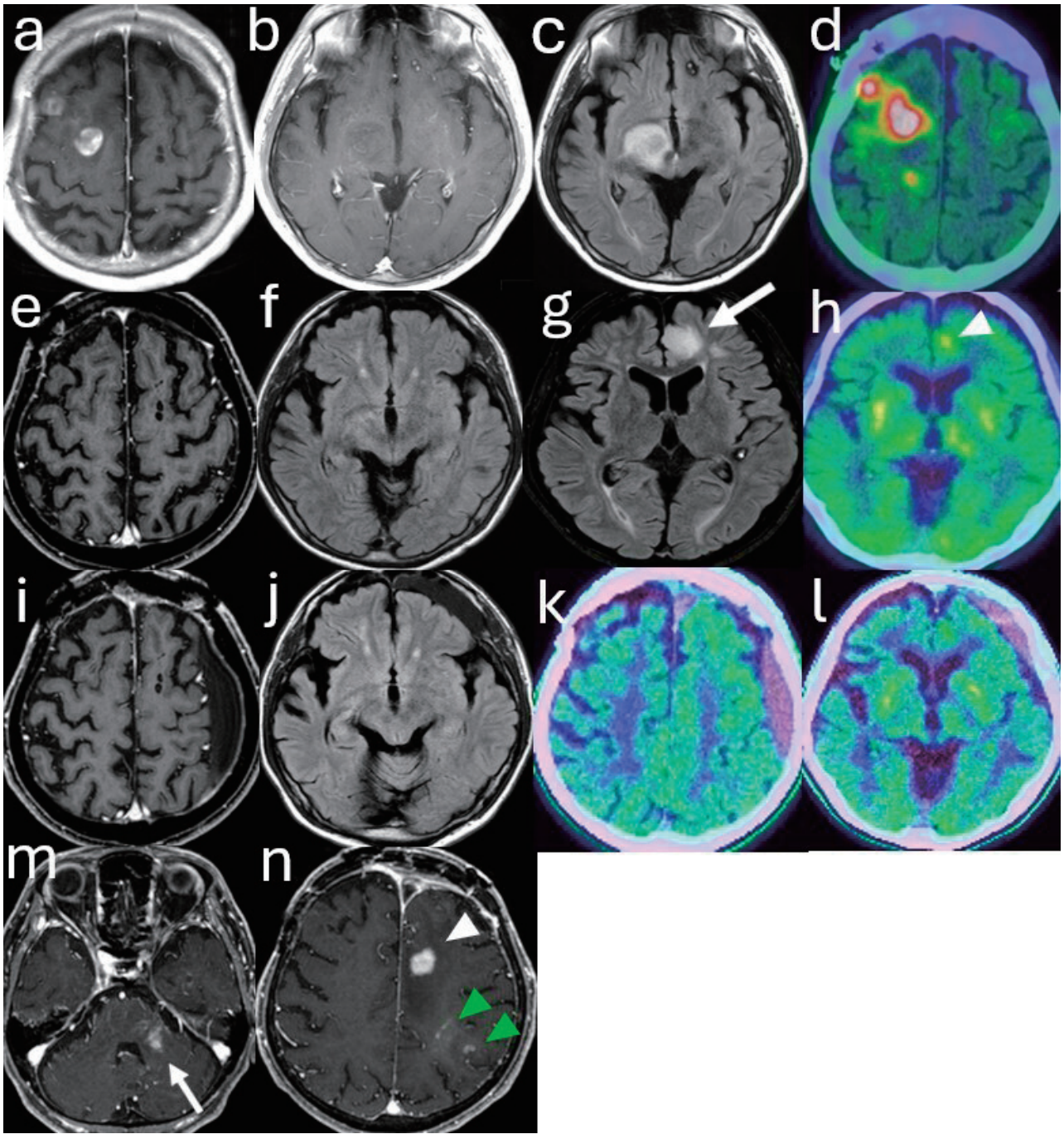

Fig. 1 MRI. T1-weighted gadolinium-enhanced MRI shows multiple enhancing tumors in the right frontal lobe (a) and a non-enhancing tumor involving the right thalamus and right midbrain (b), which appears hyperintense on FLAIR (c). ^{11}C-methionine PET before starting CRT shows strong uptake in the residual right frontal lobe tumor (d). MRI, three months after the completion of CRT, shows complete response in all lesions on T1-weighted gadolinium-enhancement (e) and FLAIR (f). MRI, 12 months after completion of CRT, shows a hyperintense lesion on FLAIR, suggesting recurrence in the left frontal lobe (white arrow) (g), with central uptake on ^{11}C-methionine PET (white arrowhead) (h). MRI, 22 months after the diagnosis of RIG, shows that the primary sites in the right frontal lobe, right thalamus, and midbrain maintain complete response on T1-weighted gadolinium-enhancement (i) and FLAIR (j). ^{11}C-methionine PET shows no significant uptake in previously treated sites (k, l). T1-weighted gadolinium-enhanced MRI 28 months after the diagnosis of RIG shows multiple enhancing tumor lesions in the left cerebellar peduncle (white arrow) (m), left frontal lobe (white arrowhead) (n), and left parietal lobe (green arrowhead) (n), which are suggestive of recurrence.

CRT: chemoradiotherapy; FLAIR: fluid-attenuated inversion recovery; MRI: magnetic resonance imaging; PET: positron emission tomography; RIG: radiation-induced glioma; T1: type 1

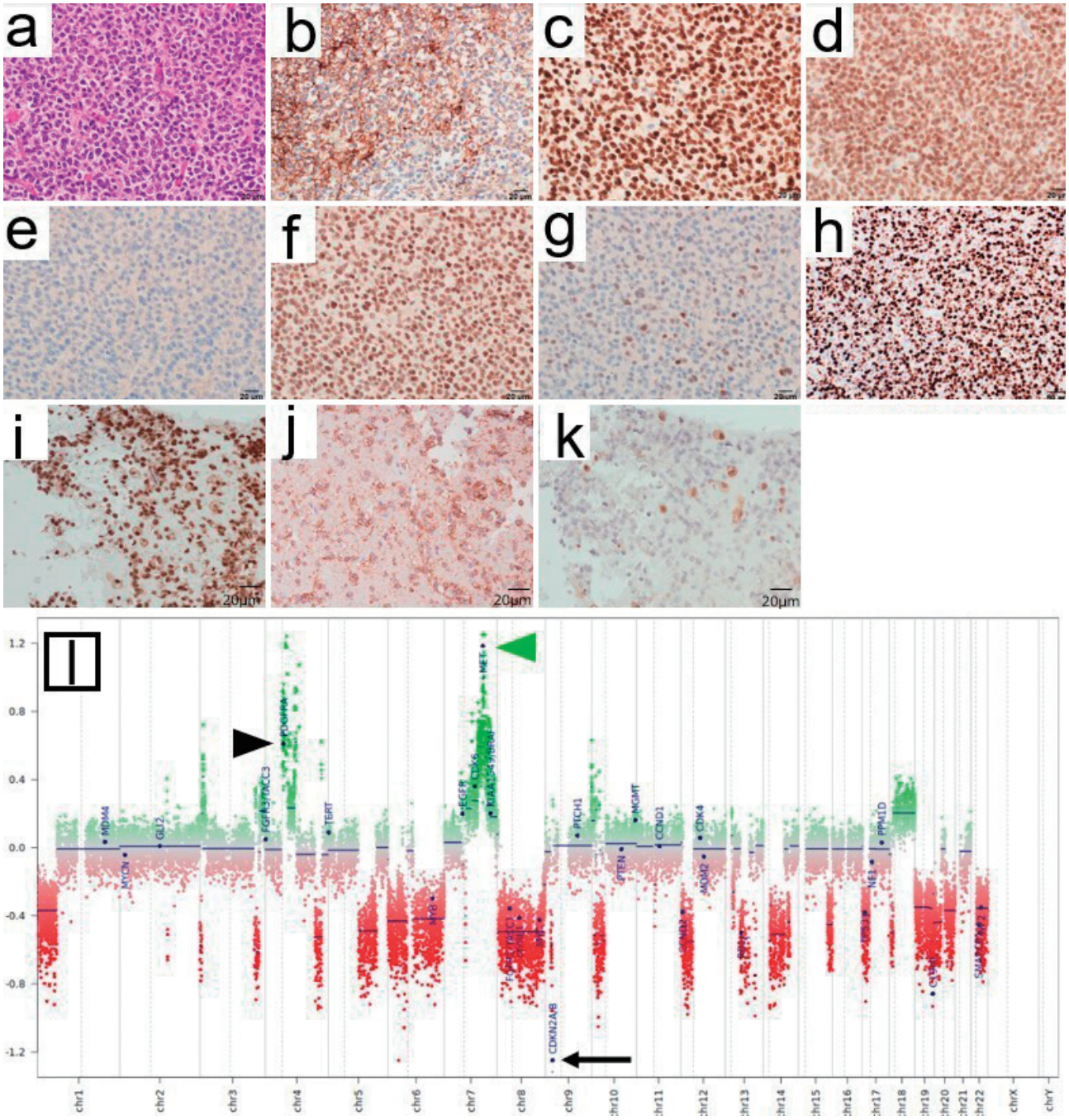

Fig. 2 Pathological features of the right frontal lobe tumor at the initial operation. H&E staining shows diffuse infiltrative proliferation of neoplastic cells with scant cytoplasm (a). The neoplasm shows immunoreactivity for GFAP (b), OLIG2 (c), and SOX10 (d). Furthermore, those neoplastic cells show no expression of IDH1 R132H (e) and preserve the nuclear expression of ATRX (f). A few neoplastic cells exhibit weak p53 nuclear expression (g). The Ki-67 labeling index is approximately 70% (h). Tumor cells were diffusely and strongly immunopositive for PDGFRA (i) and c-MET (j), with lost MTAP expression (k). The copy-number profile derived from DNA methylation array data shows significant genome-wide copy-number alterations, including *CDKN2A/B* homozygous deletion (black arrow) and *PDGFRA* amplification (black arrowhead) (l), which are often observed in RIG. *MET* amplification is also observed (green arrowhead).

ATRX: alpha-thalassemia/mental retardation syndrome X-linked; DNA: deoxyribonucleic acid; GFAP, glial fibrillary acidic protein; H&E: hematoxylin-eosin; IDH1: isocitrate dehydrogenase 1; OLIG2, oligodendrocyte transcription factor 2; RIG: radiation-induced glioma

were administered. However, MRI revealed an enlarged FLAIR hyperintense area in the left frontal lobe (Fig. 1g), with central uptake on 11C-methionine PET (Fig. 1h). He underwent a second operation 15 months after the initial surgery, and the histological diagnosis was a high-grade glioma, which could have been a relapse of an RIG or a new RIG development. The patient underwent a reduced-dose RT of 36 Gy in 18 fractions postoperatively, considering the previous irradiation history. The primary sites of the right frontal lobe, right thalamus, and midbrain maintained a complete response (Fig. 1i and j), and 11C-methionine PET showed no significant uptake in previously treated sites (Fig. 1k and l). The patient maintained a favorable performance status (PS). However, 28 months post-RIG diagnosis, the MRI showed multiple tumors in the left middle cerebellar peduncle, left frontal lobe, and left parietal lobe, suggestive of recurrence (Fig. 1m and n). The patient received stereotactic RT: 20 Gy in 5 fractions to the cerebellar peduncle lesion, 30 Gy in 5 fractions to the frontal lobe lesion, and 27 Gy in 3 fractions to the parietal lobe. Additionally, he initiated bevacizumab treatment. He is currently continuing bevacizumab treatment and is alive 30 months after the diagnosis of RIG.

Discussion

Two recently published papers by Deng et al.[6] and DeSisto et al.[5] summarized the results of comprehensive genetic analyses of more than 30 cases of RIG. These studies consistently found that RIG usually lacks typical mutations in the glioma-associated oncogenic driver genes coding for histone 3 variants, *IDH1/2*, and *BRAF*, whereas *PDGFRA* amplification and *CDKN2A/B* deletion, the representative molecular events during the progression of sporadic GBM,[13] are the most common CNAs in RIG. Furthermore, DNA methylation profiling revealed that RIG mostly clustered within the pedGBM_RTK1 methylation group.[5,6] Other frequent CNAs in RIG included *MET* amplification and *CDK4* amplification, detected in around 20% of cases in both cohorts studied by Deng et al.[6] and DeSisto et al.[5] Extensive CNAs of chromosomal units, including 1p deletion, 1q gain, 13q deletion, and 14q deletion, were present in approximately half of the RIG cases in both cohorts. Additionally, 6q deletions were found in over half of the cases in Deng et al.'s[6] cohort and in approximately one-third of the cases in DeSisto et al.'s[5] cohort, which was also observed in our case. DeSisto et al.[5] compared RIG and sporadic pediatric high-grade gliomas in the same DNA methylation class, pediatric high-grade glioma RTK1. They found that *PDGFRA* amplification and *BCOR* deletion were the most frequent CNAs in RIG. Moreover, total CNA was significantly increased in RIG cases, suggesting elevated genomic instability.[5] Regarding the composition of CNAs, copy-number reductions rather than increases predominated in RIG,[5] aligning with the pattern of copy-number abnormalities in our case. DeSisto et al.[5] also showed that chromothripsis was more frequently observed in RIGs than in sporadic pediatric high-grade gliomas. Furthermore, they identified cases in which extrachromosomal circulating DNA (eccDNA) derived from chromothripsis caused *PDGFRA* and *CDK4* gene amplification, suggesting a potential role for eccDNA in the development of RIG.[5] These findings indicate that increased CNAs were associated with genomic instability, resulting in the alteration of oncogenes and tumor suppressor genes, thereby leading to RIG development. Fusion gene formation may also contribute to RIG development. Deng et al.[6] performed ribonucleic acid sequencing and identified fusion genes, including *PTPRZ1-MET*, *CAPZA2-MET*, *FYCO1-RAF1,* and *GFAP1-NTRK2*. Interestingly, all cases with *MET*-related fusion genes showed *MET* amplification.[6] Regarding somatic gene mutations in RIG, whole genome sequencing showed that *TP53* gene mutations were the most frequently detected (approximately 20% of cases).[5,6] Moreover, mutations in the *PDGFRA* and *NF1* genes were frequently observed.[5] Furthermore, mutations in the *CBL*, *PTPN11,* and *BCOR* genes have been detected,[5,6] suggesting aberrant signaling in RAS/MAPK pathways in RIG. Methylated *MGMT* was found in 20-30% of RIG cases, and its correlation with prognosis remains inconclusive.[5-7]

The present case exhibited *PDGFRA* amplification and *CDKN2A/B* deletion, aligning most closely with the diffuse pediatric high-grade glioma RTK1 subtype according to the DNA methylation classifier, consistent with RIG molecular characteristics noted in previous studies. Additionally, this case demonstrated amplification of *KIT* and *KDR*, suggesting amplification of the 4q12 region, which has not been reported in RIG, to our knowledge. The frequency of 4q12 region amplification in sporadic GBM has been reported as 4.7%.[9] Amplification of *PDGFRA*, *KIT*, and *KDR* may serve as oncogenic drivers, and coamplification of all 3 genes has been linked to a poor prognosis in sporadic GBM.[10,14,15] Moreover, the present case also showed *MET* amplification and *EPHB4* amplification. *MET* is a proto-oncogene that encodes a protein known as HGF receptor (c-Met), an integral plasma membrane RTK. Its ligand, HGF, binds to c-Met and activates the c-Met signaling pathway, resulting in increased cell motility, infiltrative growth, angiogenesis, and resistance to apoptotic signals.[16] *MET* amplification was found in 5% of grade 4 gliomas, but not in lower grades, suggesting an association with an aggressive phenotype.[17] The *EPHB4* gene encodes an RTK, EphB4, which regulates various biological processes associated with the malignant properties of cancer cells, such as proliferation and invasion.[18]

Table 1 summarizes representative series and case reports in which survival and molecular data are available for RIG cases.[2,5,6,19] Most RIG cases had a dismal prognosis, while some had a favorable prognosis. The Deng et al.[6] cohort included one patient with *PDGFRA* amplification and

Table 1 Representative series and case reports of RIGs for which survival and molecular data are available

Authors, year, Reference	Study Type	Number of patients	Treatment	OS (months)	*IDH-1/2* status	*MGMT* methylation status	*CDKN-2A/B* del	*PDGFR-A* amp	*KIT* amp	*KDR* amp	*MET* amp	Other
Deng et al. 2021[6]	Series	32	NA	2-18*	Wild-type in all cases	Methylated: 34.6% (9/26)	65.6% (21/32)	53.1% (17/32)	NA	NA	28.1% (9/32)	*CDK4* amp 15.6% (5/32)
DeSisto et al. 2021[5]	Series	32	RT: 7 CMT: 2 Resection: 2 Resection+RT: 1 Unknown: 20	median OS: 9	Wild-type in all cases	Methylated: 25.8% (8/31)	34.3% (11/32)	46.9% (15/32)	NA	NA	9.4% (3/32)	*CDK4* amp 15.6% (5/32)
Trkova et al. 2024[2]	Series	12	TMZ+RT 45-60 Gy: 6 TMZ alone: 1 Bev: 1 None: 2 Other: 2	median OS: 7.3 (range 2-108)**	Wild-type in all cases	NA	55.6% (5/9)	44.4% (4/9)	NA	NA	NA	*CDK4* amp 11.1% (1/9)
Grogan et al. 2023[19]	Case report	2	Resection, TMZ50 mg/m^2+RT60 Gy, Standard-dose TMZ maintenance therapy	24, alive	Wild-type	Methylated	Yes	Yes	Yes	NA	NA	NA
			Resection, RT40.05 Gy, RT30 Gy, 25 Gy for spinal recurrence	17, dead***	Wild-type	Unmethylated	Yes	Low-level amp	No	No	No	NA
Present case	Case report	1	Partial resection, TMZ75 mg/m^2+RT50 Gy, 36 Gy, Standard-dose TMZ maintenance therapy, Re-resection and RT36 Gy for recurrence, SRT and Bev for 2nd recurrence	30, alive	Wild-type	Unmethylated	Yes	Yes	Yes	Yes	Yes	*EphB-4* amp

RIG, radiation-induced glioma; OS, overall survival; MGMT, O6-methylguanine-DNA methyltransferase; del, deletion; amp, amplification; NA, not available; RT, radiotherapy; CMT, chemotherapy; TMZ, temozolomide; SRT, stereotactic radiotherapy; Bev, Bevacizumab

* Seventeen of 19 evaluable patients died.

** Two patients were alive with OS of 99, 108 months.

*** The patient died 17 months after the completion of the radiotherapy without evidence of recurrence at the primary site.

CDK4 amplification but without *CDKN2A/B* deletion, who was alive at 18 months. *MGMT* status was unmethylated.[6] Another cohort by Trkova et al.[2] included 2 very long-term survivors. One patient was histologically diagnosed with gliomatosis cerebri, treated with RT and TMZ, and survived for 108 months; no molecular data were available in this case. The other patient survived for 99 months, was treated with CRT, and had molecular features of *CDKN2A/B* deletion and *BRAFV600E* mutation. The methylation class was determined to be pleomorphic xanthoastrocytoma. The *MGMT* status was unknown for both patients.[2] Interestingly, Grogan et al.[19] recently reported 2 cases of RIG exhibiting a complete response after first-line therapy. One showed molecular features similar to our case, including *CDKN2A/B* deletion, *PDGFRA* amplification, and *KIT* amplification. Contrastingly, the *MGMT* promoter was methylated, unlike our case, which may have contributed to the complete response to CRT with TMZ. However, in the other case with *CDKN2A/B* deletion and low-level amplification of *PDGFRA*, *MGMT* was unmethylated, and a

complete response was achieved with RT alone.[19] Taken together, factors other than *MGMT* methylation may be associated with treatment response and prognosis in RIG.

In conclusion, the present case exhibited a DNA methylation profile typical of RIG, and, in addition, NGS analysis showed amplification of multiple RTK-encoding genes, which are associated with worse outcomes in sporadic GBM, suggesting a more aggressive phenotype. Nevertheless, conventional CRT resulted in the resolution of multiple lesions on contrast-enhanced MRI and 11C-methionine PET, and the patient has survived for over 2 years, albeit with recurrence. This indicates that some RIGs may have distinct molecular characteristics influencing therapeutic response, differing from those of sporadic GBM, thereby underscoring the importance of accumulating clinical and molecular data to enhance molecular understanding of this rare entity.

Acknowledgments

The authors would like to thank Kayoko Kanegae for technical assistance with the experiments and Editage (www.editage.jp) for English language editing.

Author Contributions

DT and MS contributed equally to this work and were designated cofirst authors. DT managed the patient and drafted the paper. MS designed and conceptualized the work, performed next-generation sequencing and methylation profiling, prepared all figures and a table, performed a literature search, and wrote the main manuscript text. KS, MF, and RM managed the patient and provided the clinical and radiological data. TO, TE, MKM, and AS performed Sanger sequencing and methylation-specific polymerase chain reaction. TH reviewed the pathological specimen and revised the manuscript. KM, TS, and SK revised the manuscript. All the authors have read and approved the final version of the manuscript.

Funding

This work was supported in part by JSPS KAKENHI Grant Number JP19K09535.

Availability of Data and Materials

Microarray data are deposited in the Gene Expression Omnibus (GEO) under accession number GSE276059. https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE276059

Gene variant data and clinical information are registered in the C-CAT system, the Japanese genome information database. C-CAT Accession Number is EC00253286.

All other relevant data and materials related to this study are available upon reasonable request from the corresponding author (MS: mitsira@gmail.com).

Ethics Approval

This case report was approved by the Human Ethics Committee of Saitama Medical University International Medical Center (Approval number: 2024-021).

Consent to Participate

A written consent was provided by the patient to be reported in this case report.

Consent for Publication

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Declaration of Generative AI and AI-assisted Technologies in the Writing Process

The authors did not use AI or AI-assisted tools.

Conflicts of Interest Disclosure

All authors have no conflict of interest.

References

1) Leary JB, Anderson-Mellies A, Green AL. Population-based analysis of radiation-induced gliomas after cranial radiotherapy for childhood cancers. Neurooncol Adv. 2022;4(1):vdac159. doi: 10.1093/noajnl/vdac159
2) Trkova K, Sumerauer D, Bubenikova A, et al. Clinical and molecular study of radiation-induced gliomas. Sci Rep. 2024;14(1):3118. doi: 10.1038/s41598-024-53434-0
3) Paulino AC, Mai WY, Chintagumpala M, et al. Radiation-induced malignant gliomas: is there a role for reirradiation? Int J Radiat Oncol Biol Phys. 2008;71(5):1381-7. doi: 10.1016/j.ijrobp.2007.12.018
4) Neglia JP, Robison LL, Stovall M, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2006;98(21):1528-37. doi: 10.1093/jnci/djj411
5) DeSisto J, Lucas Jr JT, Xu K, et al. Comprehensive molecular characterization of pediatric radiation-induced high-grade glioma. Nat Commun. 2021;12(1):5531. doi: 10.1038/s41467-021-25709-x
6) Deng MY, Sturm D, Pfaff E, et al. Radiation-induced gliomas represent H3-/IDH-wild type pediatric gliomas with recurrent PDGFRA amplification and loss of CDKN2A/B. Nat Commun. 2021;12(1):5530. doi: 10.1038/s41467-021-25708-y
7) Whitehouse JP, Howlett M, Federico A, et al. Defining the molecular features of radiation-induced glioma: a systematic review and meta-analysis. Neurooncol Adv. 2021;3(1):vdab109. doi: 10.1093/noajnl/vdab109

8) López GY, Van Ziffle J, Onodera C, et al. The genetic landscape of gliomas arising after therapeutic radiation. Acta Neuropathol. 2019;137(1):139-50. doi: 10.1007/s00401-018-1906-z
9) Disel U, Madison R, Abhishek K, et al. The pan-cancer landscape of coamplification of the tyrosine kinases KIT, KDR, and PDGFRA. Oncologist. 2020;25(1):e39-47. doi: 10.1634/theoncologist.2018-0528
10) Dono A, Ramesh AV, Wang E, et al. The role of *RB1* alteration and 4q12 amplification in IDH-WT glioblastoma. Neurooncol Adv. 2021;3(1):vdab050. doi: 10.1093/noajnl/vdab050
11) Cahan WG, Woodard HQ, Higinbotham NL, et al. Sarcoma arising in irradiated bone; report of 11 cases. Cancer. 1948;1(1):3-29. doi: 10.1002/1097-0142(194805)1:1<3::aid-cncr2820010103>3.0.co;2-7
12) Capper D, Jones DTW, Sill M, et al. DNA methylation-based classification of central nervous system tumours. Nature. 2018;555(7697):469-74. doi: 10.1038/nature26000
13) Sottoriva A, Spiteri I, Piccirillo SGM, et al. Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. Proc Natl Acad Sci U S A. 2013;110(10):4009-14. doi: 10.1073/pnas.1219747110
14) Carlotto BS, Trevisan P, Provenzi VO, et al. PDGFRA, KIT, and KDR gene amplification in glioblastoma: heterogeneity and clinical significance. NeuroMolecular Med. 2023;25(3):441-50. doi: 10.1007/s12017-023-08749-y
15) Burford A, Little SE, Jury A, et al. Distinct phenotypic differences associated with differential amplification of receptor tyrosine kinase genes at 4q12 in glioblastoma. PLoS One. 2013;8(8):e71777. doi: 10.1371/journal.pone.0071777
16) Yi S, Tsao MS. Activation of hepatocyte growth factor-met autocrine loop enhances tumorigenicity in a human lung adenocarcinoma cell line. Neoplasia. 2000;2(3):226-34. doi: 10.1038/sj.neo.7900080
17) Kwak Y, Kim SI, Park CK, et al. C-MET overexpression and amplification in gliomas. Int J Clin Exp Pathol. 2015;8(11):14932-8.
18) Bhatia S, Bukkapatnam S, Van Court B, et al. The effects of ephrinB2 signaling on proliferation and invasion in glioblastoma multiforme. Mol Carcinog. 2020;59(9):1064-75. doi: 10.1002/mc.23237
19) Grogan PT, Helgager JJ, Deming DA, et al. Case report: radiographic complete response of radiation-induced glioblastoma to front-line radiotherapy: a report and molecular characterization of two unique cases. Front Neurol. 2023;14:1099424. doi: 10.3389/fneur.2023.1099424

Corresponding author: Mitsuaki Shirahata, MD, PhD.
Department of Neurosurgery/Neuro-oncology, Saitama Medical University International, Medical Center, 1397-1 Yamane, Hidaka, Saitama 350-1298, Japan.
e-mail: mitsira@gmail.com