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Systemic Metastasis of Pediatric Diffuse High-grade Astrocytoma: A Case Report

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Abstract

Extracranial brain tumor metastases are extremely rare. The etiology, pathophysiology, and clinical progression of systemic metastatic brain cancer remain to be elucidated. We encountered a case of pediatric diffuse high-grade astrocytoma in a four-year-old girl with subcutaneous and lymph node metastases. Numerous metastatic lesions emerged, progressed rapidly, and were difficult to manage despite temozolomide (TMZ) administration. The patient underwent repeated surgical resection for these lesions. Conversely, the primary intracranial lesions responded well to TMZ for some time. However, the patient died 15 months after the initial diagnosis. Extracranial metastasis and highly varying effects of chemotherapy were the characteristic clinical features in this case. Our analysis did not reveal definitive histopathological and molecular factors contributing to this presentation. The lack of notable molecular pathological features illustrates the unpredictability of glioma metastasis, and the treatment for extracranial metastasis remains unknown. A gene panel analysis revealed several genetic aberrations, including *PDGFRA*, *PIK3CA*, and *NBN* mutations. As it is impossible to resect all frequently and rapidly progressing lesions, we stress that the prognosis of metastatic brain tumors is undoubtedly poor if these tumors are refractory to existing treatments, including chemotherapy.

Keywords: astrocytoma, central nervous system, metastasis, malignant glioma

Introduction

Systemic glioma metastasis is extremely rare.[1-3] Brain tumor cells rarely migrate, engraft, and grow outside the skull, although physicians occasionally encounter intracranial dissemination of glioma.[3,4]

Herein, a case of systemic metastasis of pediatric diffuse high-grade astrocytoma (HGA) was described in a four-year-old girl who underwent two surgical resections for a left temporal lobe tumor presenting with radical progression of extracranial metastatic lesions. We report this patient's clinical course and the results of molecular histopathological examinations.

Case Report

A previously healthy four-year-old girl presented to her local hospital with persistent headaches and vomiting. She had a family history of breast and uterine cancer. Head computed tomography (CT) and magnetic resonance imaging (MRI) of the head revealed a well-demarcated tumor in the left temporal lobe homogenously enhanced with a gadolinium (Gd) contrast agent (Fig. 1-a, b). She underwent initial surgical resection at her local hospital, resulting in subtotal resection (Fig. 1-c). A second surgical resection was performed at our tertiary care center two months after the initial surgery due to the residual tumor progression, and gross total resection was achieved at the second surgery (Fig. 1-d).

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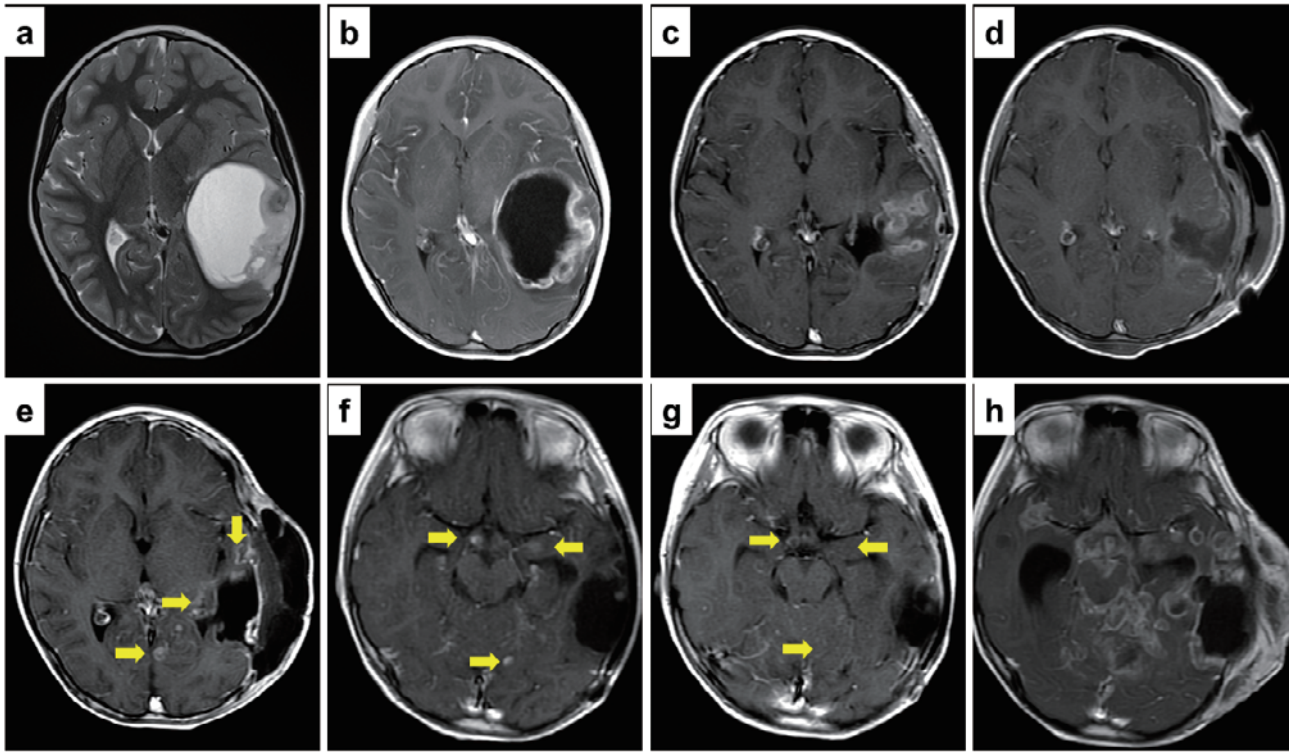

Fig. 1 Time course of neuroimaging findings of intracranial lesions.
This figure illustrates the time course of neuroimaging findings (a) initial recognition on T2WI, (b) initial recognition on T1WI with contrast-enhanced mater (Gadolinium) (T1-Gd), (c) after the first surgical resection on T1-Gd at the previous hospital, (d) after the second surgical resection on T1-Gd at our hospital, (e) at recurrence on T1-Gd, (f) T1-Gd before prescribing temozolomide, (g) one month after prescribing temozolomide on T1-Gd, and (h) at dissemination on T1-Gd.
Abbreviations: T2WI, T2 weighted imaging; T1WI, T1 weighted imaging; Gd, gadolinium

Histopathological findings of two nearly identical specimens taken from the patient's first and second surgical resections were consistent with pediatric diffuse HGA (*isocitrate dehydrogenase-1* [*IDH-1*] wild-type) (Fig. 2-a). The findings revealed dense atypical cell aggregation in a partly myxomatous background, with several vessels showing marked microvascular proliferation (Fig. 2-a). Some atypical cells presented with a halo around the nuclei, showing an oligodendroglioma-like area (Fig. 2-b).

On immunohistochemistry (IHC), the atypical cells were positive for GFAP (glial fibrillary acidic protein; focal) (Fig. 2-c), nestin (focal), synaptophysin (focal), S-100 beta (focal), Olig2 (oligodendrocyte transcription factor 2), ATRX (alpha thalassemia X-linked mental retardation; wild-type), INI1 (wild-type), and H3K27 me3 (wild-type) and negative for epithelial membrane antigen, L1CAM (L1 cell adhesion molecule), IDH-1-R132H, p53, and H3K27M. MIB-1 labeling index was estimated at 70%-80% (Fig. 2-d). The status of 1 p/19q was checked in the specimen from the second surgical resection, revealing a gain of 1q and 19q.[5] Tumor tissue collected from the intracranial region during the second surgery was analyzed using a FoundationONE assay (Foundation Medicine, Cambridge, MA, USA) (Table 1).

The patient then underwent extended focal radiotherapy at a dose of 54 Gray, concomitant with temozolomide (TMZ) at 75 mg/m^2.[6] Routine MRI check-ups were conducted every two to three months after the second surgery. There had been no sign of recurrence until several months after the second surgery when she and her parents recognized a palpable bulge under the skin near the incision site. The lesion was tiny and elastic, without pain, rash, or tenderness in the skin. No evidence of recurrence within the intracranial region was observed. However, the lesion grew drastically over the next several weeks, eventually causing a rash and skin tenderness (Fig. 3-a). MRI demonstrated high intensity on diffusion-weighted imaging with ring enhancement using a Gd contrast agent, which we suspected to indicate inflammation or infected atheroma (Fig. 3-b, c). Simultaneously, her parents recognized a palpable node around her neck (Fig. 3-e).

She underwent surgical resection and curettage of the subcutaneous lesion. Pathological findings revealed metastasis of pediatric diffuse HGA (Fig. 2-e). The subcutaneous lesion was soft and grayish in color, encapsulated by a thick membrane, and located between the galea and the periosteum.

Fluorodeoxyglucose positron emission tomography (FDG-PET) performed soon after the resection of the sub-

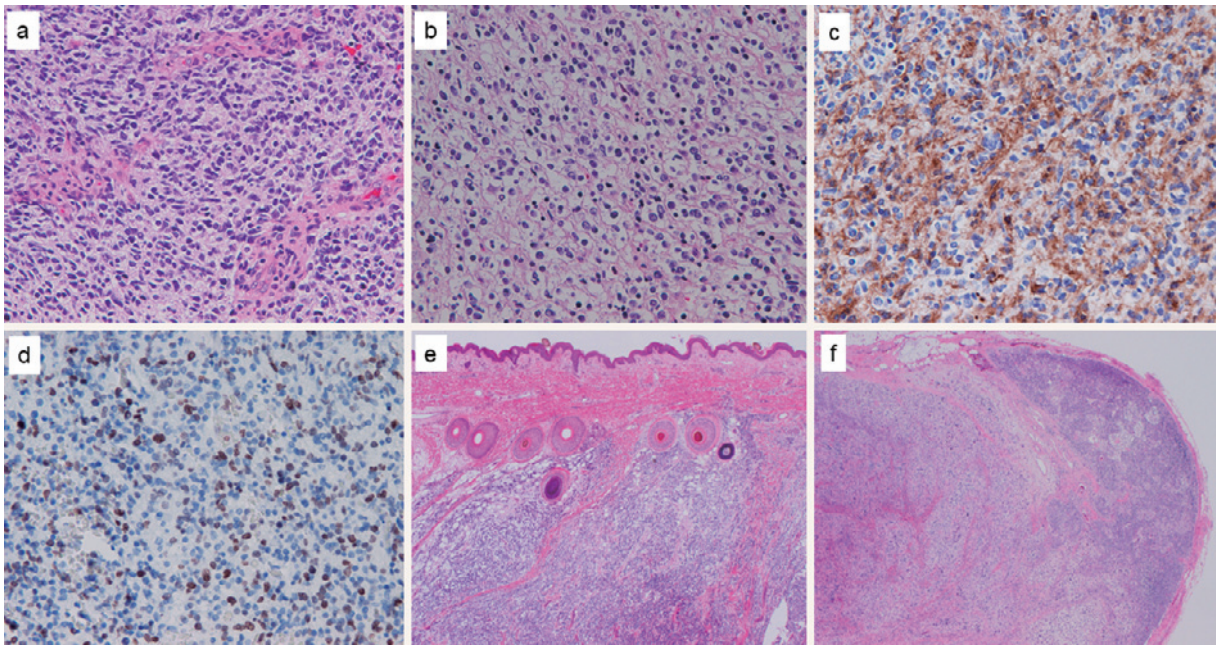

Fig. 2 Histopathological findings of the original lesion.
H&E staining of (a) a surgically resected specimen from the intracranial region, (b) the oligodendroglioma-like component, (c) GFAP findings, (d) MIB-1 labeling index. H&E staining of (e) a surgically resected specimen from the subcutaneous region (low magnification), and (f) a surgically resected specimen from the lymph nodule (low magnification).
Abbreviations: H&E, hematoxylin, and eosin; GFAP, Glial fibrillary acidic protein

Table 1 The result of gene panel analysis

Gene panel analysis			
Microsatellite	Mutations	Amplifications	Deletion
Stable	*NBN* (p.I171V)	*CDK4* (12q14.1)	Not detected
	BRIP1 (p.R814C)	*MDM2* (12q15)	
	NOTCH1 (p.T1573A, p.G2306D)		
	NOTCH3 (p.A1450T)		
	PDGFRA (p.N659K)		
	PIK3CA (p.N157S)		

cutaneous lesion for systemic evaluation revealed pathological accumulation at the cervical lymph node (Fig. 3-f). Subsequently, the patient underwent lymph node dissection and the insertion of an implanted central venous catheter (Fig. 3-g). As with the subcutaneous lesion, the pathology of the examined lymph nodes confirmed the presence of metastasis from pediatric diffuse HGA (Fig. 2-f). No histopathologic differences were evident between the intra- and extracranial lesions.

MRI conducted seven months after the second resection surgery showed dissemination in the intracranial region and spine (Figs. 1-e and 3-d). We prescribed additional spinal irradiation and intravenous TMZ injections at 150 mg/m^2 for five days, followed by 23 days of rest. Despite this treatment being highly effective in managing the intracranial disseminated lesions, there was regrowth of subcutaneous lesions metastasized, and new palpable lymph nodes emerged (Fig. 1-f, g). She underwent two additional surgical resections for subcutaneous lesions with marginal skin tissue involvement. These extracranial lesions comprise grayish soft tumor tissue, with some areas showing yellowish and slightly elastic characteristics rather than soft tissue within the lesions (Fig. 3-h). However, controlling the intracranial disseminated, subcutaneous metastatic, and lymph node lesions became increasingly difficult (Fig. 1-h). Finally, at the age of five years (15 months after her initial diagnosis), the patient succumbed to the primary disease. Written informed consent was obtained from the patient's family to publish her anonymized medical findings and accompanying images.

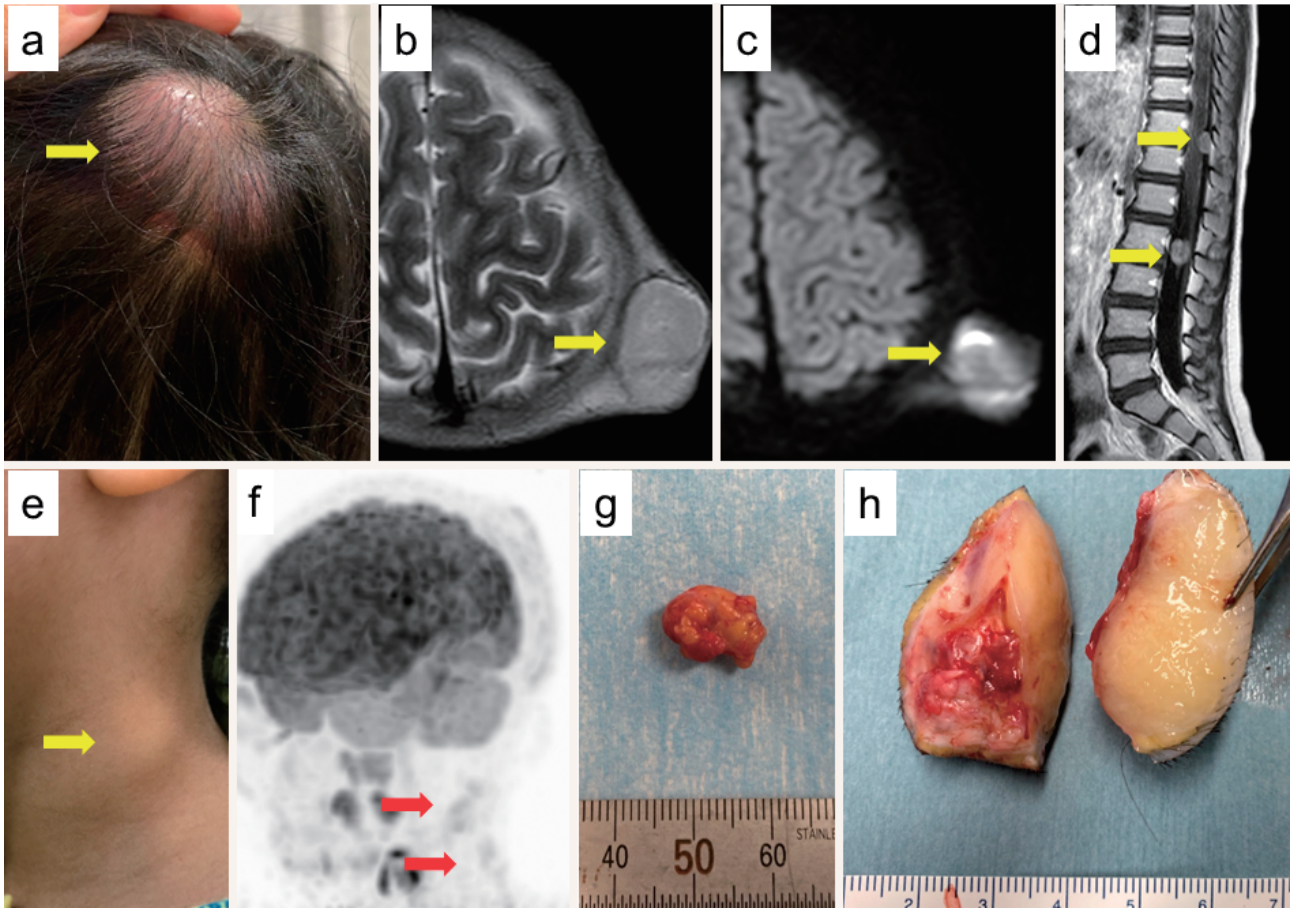

Fig. 3 Physical, macroscopic appearance, and neuroimaging of metastatic lesions and spine dissemination.
This figure illustrates (a) the physical appearance of a metastatic subcutaneous lesion, (b) MRI findings of the subcutaneous lesion on T2WI, (c) the subcutaneous lesion on DWI, (d) spine MRI with contrast-enhanced mater. (e) This figure illustrates the physical appearance of metastatic lesions at the cervical region, (f) FDG-PET images, (g) resected tissue from the cervical region. Tumor tissue from the resection surgery for subcutaneous lesions, and (h) microscopic views of subcutaneous tissue (the tumor consisted of grayish soft tumor tissue, and yellowish, relatively hard, oily tissue, and tumors existed between the galea and periosteum spine at the time of initial recognition.)
Abbreviations: DWI, diffusion-weighted imaging; FDG-PET, fluorodeoxyglucose positron emission tomography

Discussion

The incidence rate of GBM metastasis in adults is approximately 0.2%-2.0%.[7-9] However, background information regarding metastasis in pediatric cases is currently unavailable.

According to reviews of published reports on glioma metastasis, the lung is the most common metastasis site, followed by the lymph nodes.[1,2,7,10,11] A few reports have described metastases to other sites, including the liver, parotid glands, subcutaneous skin layers, and bone marrow.[2,4,7,10-15] Therefore, systemic metastasis evaluation must be performed if metastasis is suspected based on clinical examinations.[4,8,9,16] For instance, if physicians detect palpable lymph nodes or mass lesions around the surgical field on physical examination or if the excised specimens around the surgical field reveal the same pathological findings as the intracranial lesion, it is critical to suspect systemic metastasis rather than simply concluding that the finding is a drop metastasis in the surgical field.[1,9]

Full-body CT scans and/or FDG-PET are effective methodologies for identifying systemic metastasis.[1,8] Metastasis of glioma to the extracranial region occurs extremely infrequently due to the absence of lymphatic vessels in the intracranial region, the presence of the blood-brain barrier (BBB), and the specific clinical characteristics of GBM.[7,8] It is generally considered that lymph node metastasis occurs through tumor cell infiltration via disrupted dura mater or scalp due to surgical procedures.[17-19] However, the recent discovery of the dural lymphatic network may explain the presence of lymph node metastasis even in patients who have not undergone surgery.[17,18] Additionally, in this case, systematic metastasis occurred in an extremely short period (approximately eight months after surgery), suggesting

that the duration between interventions could not solely determine extracranial metastasis.[3,4,7,11]

Given the rarity of systemic metastasis in this cancer type, a detailed comparative pathological examination was conducted to determine the differences between the presentation in the current case and ordinary pediatric diffuse HGA. No definitive factors contributing to metastasis were identified in our case. However, this fact can indicate that GBM metastasis outside the skull is unpredictable and might occur even without notable histopathological findings. Thus, metastasis may occur much more frequently than expected or reported.[15,20]

A significant difference in the therapeutic effects of TMZ on intra- and extracranial lesions was another characteristic clinical feature of this case, along with extracranial metastasis. For instance, disseminated recurrence within the intracranial region first occurred within approximately 10 months after gross total resection, and administering TMZ was highly effective in addressing these lesions. In contrast, the extracranial metastatic lesions progressed rapidly despite TMZ administration, and new lesions emerged at other sites. We analyzed methylguanine methyltransferase (MGMT) status by IHC on lesions obtained from each surgical site to investigate the reason for the differential response to TMZ. However, no differences were found in the MGMT status between the lesions from the three identical regions; all showed partial positivity for MGMT. Furthermore, it is generally believed that extracranial lesions tend to be more responsive to therapeutic modalities than intracranial lesions due to the absence of the BBB, as previously reported.[21] Surprisingly, the intracranial lesions exhibited a significantly better response in the present case. However, the underlying reason for this remains unknown due to limited literature addressing the disparity in chemotherapy response between intra- and extracranial lesions.

Furthermore, a gene panel analysis was conducted on the specimen obtained from the second tumor resection, revealing several genetic aberrations. Herein, we focused on *PDGFRA* and *NBN* mutations.

Evaluation of *PDGFRA* gene aberrations and their clinical significance in cases of high-grade gliomas (HGGs) have been previously reported.[22] For example, Verhaak et al. retrospectively analyzed and classified adult GBM into three sub-groups: a pro-neural type comprising tumors with the major features of *PDGFRA* alterations, *IDH-1* point mutations, and high expression of *Olig2* (an oligodendrocytic development gene).[23] In our case, a *PDGFRA* point mutation and oligodendroglial differentiation were consistent with the features of the pro-neural type. However, the absence of an *IDH-1* mutation was inconsistent with this presentation, possibly reflecting differences in the incidence of *IDH-1* mutations between pediatric and adult cases.[24] In addition, Verhaak et al. reported that tumors with *PIK3CA/PIK3R1* mutations showed no evidence of *PDGFRA* mutations, inconsistent with the postulated subtype.[23] Hence, these facts indicate that this sub-grouping is well-categorized for adult GBM but is not entirely applicable to pediatric cases with different genetic backgrounds.

In contrast, Mackay et al. analyzed pediatric HGG and diffuse intrinsic pontine glioma cases demonstrating histone H3*/IDH-1* wild-type genetic profiles and found that enrichment for chromosome 1p, 20q loss, 17q gain, *PDGFRA* mutations, and *MET* amplifications led to classification into the wild-type-C group, nearly corresponding to the pro-neural type.[23,24] *PDGFRA* mutations are the hallmark of pediatric HGG and can influence tumorigenesis, cell differentiation, and aggressive clinical behavior.[22-25] However, based on the current data and overall evidence, drawing a definitive conclusion is difficult as to whether a specific tumor subtype contributed to the patient's metastasis state.

Furthermore, *NBN* mutations are genetic alterations that cause genomic instability and carcinogenesis through the Nijmegen breakage syndrome.[26-28] In brain tumors, the presence of *NBN* mutations has been discussed in one case of medulloblastoma, and there have been several reports of GBM and ganglioglioma presenting with *NBN* gene mutations.[26,27] Since only a single illustrative case report was presented, drawing definitive conclusions is difficult (as is the case for *PDGFRA*) regarding whether *NBN* aberrations affect the incidence of metastasis or lead to differences in the effectiveness of TMZ. Along with the gene mutations mentioned earlier, numerous other genetic aberrations associated with metastasis have been reported in all types of cancer, including intracranial and all other organs. Therefore, cross-sectional gene panel analysis has proven valuable in detecting such genetic aberrations, even though its relevance may have been previously overlooked.[17,29-32] Future studies involving a larger cohort of pediatric HGA cases must elucidate the correlation between metastasis, treatment sensitivity, and specific genetic aberrations.

The optimal treatment for metastatic glioma remains unknown.[4,16] Some reports recommend radiotherapy, chemotherapy, molecular targeting agents, surgical resection, or a combination of these for metastatic lesions.[1-4,7,11,15,16] However, it is generally impossible to resect all lesions in cases with multiple metastases during surgical resection. Moreover, unlike other parts of the body, the extensibility of the scalp is undoubtedly limited, requiring broader skin implantation if the extent of the area for resection becomes wider (as was seen in this case). Currently, treatment for metastatic lesions is extremely limited.[4,11] Therefore, the prognosis for metastatic brain tumors remains poor.[7,16]

In conclusion, metastasis of glioma could be a possible clinical event, and glioma cases should be monitored accordingly. In this case, the therapeutic response to TMZ showed meaningful differences between intra- and extracranial lesions. However, no definitive histopathological,

neuroimaging, or genetic factors were identified when comparing three equivalent specimens from primary, subcutaneous, and lymph node lesions. Our findings, which must be confirmed in future case series and high-powered epidemiologic studies, inform research directions and medical guidelines.

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Statement of Ethics

This report was written following the Declaration of Helsinki. Since this was a case report, the institutional review board waived the requirement for informed consent. To protect patient confidentiality, we removed all identifiers from our records.

Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

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