Child's Nervous System (2019) 35:2047–2054
https://doi.org/10.1007/s00381-019-04372-0

CASE-BASED UPDATE

The molecular oncology of bilateral high-grade thalamic astrocytomas in children

Amir Goodarzi[1] · Nicholas Garza[2] · Mirna Lechpammer[3] · Reuben Anthony[4] · Marike Zwienenberg[1]

Received: 14 November 2018 / Accepted: 4 September 2019 / Published online: 14 September 2019

Abstract

Background Bilateral thalamic astrocytomas in children are exceedingly rare. These highly malignant tumors seldom respond to conventional treatment strategies and carry a grim prognosis for patients. However, recent advances in molecular oncology have had a positive impact on prognostication and treatment strategies of these tumors.

Case-based review We present a new case of WHO grade III bilateral thalamic astrocytoma in a child and review the pathophysiology, molecular oncogenesis, and relevant treatment strategies for this rare disease.

Conclusions High-grade thalamic astrocytomas affecting both thalami pose a challenge to pediatric neurosurgeons, neuro-oncologists, and neuropathologists given the lack of effective treatment strategies. Understanding recent revelations in the field of molecular oncology can assist clinicians in adequately formulating a treatment plan in this patient population.

Keywords Molecular · Oncology · Histones · Glioma

Introduction

Bilateral thalamic astrocytomas in children are uncommon tumors that carry an unfavorable prognosis. Literature on the epidemiology, natural history, and pathogenesis of these tumors is limited, and only a handful of small case series and reports exist on this topic [1–3]. The majority of bilateral thalamic astrocytomas in children are low grade; however, there are rare cases of bilateral high-grade tumors [2, 3]. To our knowledge, only 49 cases of pediatric bilateral thalamic astrocytomas have been reported, which include six cases of WHO grade IV and seven cases of WHO grade III astrocytomas (Table 1). We present a case of bilateral thalamic WHO grade III astrocytoma in a child and review the pathophysiology, oncogenesis, relevant molecular markers, and treatment strategies for this rare disease.

✉ Amir Goodarzi
agoodarzi@ucdavis.edu

[1] Departments of Neurological Surgery, University of California, Davis, Sacramento, CA, USA

[2] School of Medicine, University of California, Davis, Sacramento, CA, USA

[3] Department of Pathology, University of California, Davis, Sacramento, CA, USA

[4] Department of Pediatric Hematology-Oncology, University of California, Davis, Sacramento, CA, USA

Historical background

High-grade bilateral thalamic astrocytomas present significant diagnostic and therapeutic challenges to pediatric neurosurgeons, neuro-oncologists, and neuropathologists on account of their rarity, location, small amount of resultant biopsy tissue, and lack of standardized therapy [1–5]. Historically, thalamic astrocytomas were deemed inoperable due to the high risk of post-operative morbidity and mortality. However, advancements in image-guidance technologies and microsurgical techniques have made radical resection of unilateral thalamic low-grade lesions a possibility [6]. In contrast, bilateral and high-grade thalamic lesions are unsuitable for surgical removal, and to date, no successful attempts of gross total resection have been reported in children [1, 3]. To address the challenges posed by bilateral thalamic astrocytomas, a multidisciplinary approach is required, incorporating molecular-oncology, histopathology, radiology, and neurosurgery. Moreover, in the past decade, molecular profiling of high-grade pediatric tumors has shed some light on their oncogenesis and has in some cases informed therapy. This article

Table 1 Survival outcomes of bilateral thalamic WHO grade IV astrocytoma in pediatric patients. *STR* subtotal resection, *CT* chemotherapy, *RT* radiation therapy, *NR* not reported

Study	Age and gender	Treatment	Survival
Broniscer et al. (2017)	2.4 years M	STR + CT	6 months
Broniscer et al. (2017)	4.8 years M	STR + RT + CT	12 months
Pandey et al. (2014)	8 years M	Biopsy, NR	12 months
Jain et al. (2013)	11 years M	Biopsy, NR	12 months
Steinbock et al. (2017)	NR (less than 17.9 years)	STR, RT, CT	10 months
Steinbock et al. (2017)	NR (less than 17.9 years)	STR, RT	37 months

reviews the relevant literature on the pathophysiology, oncogenesis, molecular biology, and management of this rare tumor.

Clinical presentation

Presenting symptoms of high-grade thalamic tumors in children commonly include headaches, nausea, and gait instability secondary to obstructive hydrocephalus and elevated intracranial pressures [1–3, 6]. These symptoms have insidious onset and may be subtle on initial presentation which makes definitive diagnosis challenging for pediatricians and primary care physicians.

Diagnosis

Imaging is essential for initial diagnosis of any intracranial mass, although biopsy-derived histopathological assessment is required for definitive diagnosis. High-grade thalamic astrocytomas in children appear as ill-defined hypodensities affecting the thalami in computed tomography. With magnetic resonance imaging, these lesions present as homogenous and well-demarcated masses that generally do not enhance with IV gadolinium contrast, although some lesions may partially enhance [1–3]. They are hypointense in T1-weighted imaging and hyperintense in T2-weighted and FLAIR sequences [1, 7]. MR spectroscopy shows an increased creatine-phosphocreatine peak that is uncommon in unilateral thalamic gliomas. Additional MR spectroscopy characteristics include an increase in choline containing compounds and a decrease in *N*-acetyl aspartate [1, 7]. The differential diagnosis for lesions involving the thalami in children include pilocytic astrocytoma, diffuse astrocytoma, oligodendroglioma, anaplastic astrocytoma, and glioblastoma [8].

Management

The World Health Organization categorizes high-grade astrocytomas as anaplastic (grade III) and glioblastoma (grade IV). Anaplastic astrocytomas exhibit marked nuclear atypia, hypercellularity, and high mitotic activity. In addition to similar hypercellularity, glioblastomas also feature necrosis or microvascular proliferation [2].

Although the exact mechanism of oncogenesis in pediatric high-grade thalamic astrocytomas remains unknown, recent advances in the field of molecular oncology have allowed for improvements in prognostication and treatment strategies. It has become increasing clear that pediatric astrocytomas appear to be genetically distinct from adult astrocytomas [3, 4]. For example, isocitrate dehydrogenase (IDH1/IDH2) mutations are typically absent in the pediatric high-grade gliomas and thus do not provide a significant prognostic value as compared to their adult counterparts [3, 4]. In the next section, we review clinically relevant molecular genetic alterations in high-grade pediatric thalamic astrocytomas and their possible roles in oncogenesis.

Histone 3 mutations

Histones are nuclear proteins that interact with DNA molecules to give rise to nucleosomes, a fundamental structural unit of chromosomes. Through their manipulation of chromosomal structure, histones can affect DNA transcription and DNA replication [9–11].

Mutations in the gene encoding for histone 3, specifically the H3.3 K27M mutation, have been observed in 20–66% of all high-grade pediatric gliomas [4, 9–11]. The H3.3 K27M mutation appears to be limited to only midline high-grade gliomas including diffuse pontine gliomas in the pediatric population and is notably absent in hemispheric gliomas and adult high-grade gliomas [4, 11]. In 2016, the revised WHO classification of tumors of the central nervous system introduced a new diagnostic category termed "diffuse midline glioma H3K27M mutant," encompassing gliomas apparently arising from midline structures including the thalamus, brainstem, and spinal cord [2]. This mutation is now being used as a diagnostic and prognostic marker for diffuse high-grade gliomas [4, 9–11]. This new category of diffuse midline glioma behaves aggressively and is automatically classified as WHO grade IV [2]. Clinically, patients whose tumors harbor the H3.3 K27M mutation appear to have a uniformly poor

overall survival when compared to wild-type tumors [4, 8, 10–12]. Interestingly, recent observations by Gupta et al. and by Broniscer et al. have revealed that H3.3 K27M mutations are uncommon in bilateral high-grade thalamic astrocytomas, suggesting a fundamental difference in the oncogenesis and molecular biology between unilateral and bilateral thalamic lesions [8, 12]. Our patient's tumor lacked the H3.3 K27M mutation, and the tumor was present in both thalami, which further corroborates the trends noted by Broniscer et al. [12].

Another histone 3 mutation, H3.3 G34 R/V, has been observed in some pediatric high-grade gliomas; however, this mutation appears to be more prevalent in hemispheric lesions and is rare in midline and thalamic astrocytomas [11, 13]. This mutation group is the only pediatric glioma group that is likely to harbor MGMT epigenetic changes and ATRX mutations, which are genetic alterations that are frequently noted in adult glial tumors [11, 13].

H3.1 K27M mutations have also been identified in pediatric midline high-grade gliomas; however, they appear to be isolated to diffuse intrinsic pontine gliomas [11, 14]. Tumors harboring the H3.1 K27M mutation were more susceptible to radiotherapy and had a more favorable clinical course compared to those with the H3.3 K27M mutation [14].

Finally, there are recent data suggesting that tumors that are wild type with respect to both histone 3 and IDH1 gene may have distinct molecular and clinical characteristics in children [11, 13]. This group of tumors appears to be predominantly composed of pleomorphic xanthoastrocytomas (PXAs) and low-grade gliomas (LGGs) with a favorable median survival of 63 months. However, even high-grade, non-PXA/LGG tumors that are wild type for IDH1 and H3 gene showed a significantly more favorable median survival of 38 months compared to non-wild type high-grade tumors [11]. Our patient's tumor falls into the category of H3 and IDH1 wild type, and despite the high-grade histopathological features, he continues to remain clinically stable at 13 months post diagnosis.

Alpha thalassemia/mental retardation syndrome X-linked

Alpha thalassemia/mental retardation syndrome X-linked (ATRX) protein is a nuclear protein that interacts with death-domain-associated protein (DAXX) and histones to remodel chromatin and telomeres. Loss of ATRX protein through mutation is thought to destabilize telomeres, and subsequently results in telomerase independent maintenance of telomeres, a process known as alternative lengthening of telomeres (ALT) [15, 16]. This process of ALT is linked to oncogenesis [17]. Although loss of ATRX and consequent ALT are common in high-grade pediatric astrocytomas, there are conflicting reports regarding their prognostic significance. Nguyen et al. noted an association between ALT-positive status and an increase in overall survival in all patients with high-grade astrocytomas [18]. Conversely, Abedalthagafi et al. noted no associations between ALT or ATRX status and overall survival [15]. As mentioned earlier in this manuscript, ATRX mutations are likely to appear in hemispheric pediatric tumors with the H3.3 G34 R/V mutation [13, 15]. There was no mutation in the ATRX gene in the patient presented in this report.

Platelet-derived growth factor receptor α

Platelet-derived growth factor receptor alpha (PDGFR α) is a transmembrane protein capable of interacting with several major signal transduction pathways in developing cells, including the PI3K/AKT, RAS/MAPK, Src kinase family, and PLC/PKC pathways [19, 20]. Through the modulation of these major signaling pathways, PDGFR α can affect gene transcription, cell growth, cell differentiation, and cell migration [19, 20]. PDGFR α amplification is a frequent molecular abnormality in high-grade pediatric gliomas, occurring in 15–39% of cases [20, 21]. Results from small series of pediatric high-grade glioma patients have linked PDGFR α mutations and amplification to a worse prognosis, although there is no direct link between bilateral thalamic astrocytomas and these mutations [22]. The patient in this report had no mutation or amplification present in the PDGFR α gene.

TP53

P53 tumor suppressor protein is a key regulator in the transcription of downstream genes involved in apoptosis, cell cycle arrest, and DNA repair [23]. The role of P53 mutations is thought to be less significant in pediatric astrocytomas than in adults, although conflicting reports exist in the literature. In some reports, mutations in the TP53 gene have been observed in 35–38% of high-grade pediatric gliomas, resulting in P53 protein overexpression in 75% of cases [3, 24]. This overexpression has been linked to a worse prognosis in pediatric high-grade gliomas [3, 24]. Conversely, others have noted a low frequency of P53 mutation in pediatric astrocytomas with no clear link to prognosis [24]. The patient presented in this report was found to have biallelic TP53 mutation and inactivation, which supports the notion that high-grade bilateral thalamic gliomas may have a distinct molecular morphology.

O^6-methylguanine-DNA-methyltransferase methylation

The O^6-methylguanine-DNA-methyltransferase (MGMT) gene encodes a DNA repair protein responsible for repairing alkylating damage to DNA [25]. Methylation of the MGMT promoter leads to gene silencing and has been linked to a better response to alkylating chemotherapeutic agents (e.g.,

temozolamide). The reported incidence of MGMT promoter methylation is highly variable in high-grade pediatric gliomas, ranging from 0 to 77% [25, 26]. However patients whose glioblastomas have methylated MGMT promoters have a much more robust response to chemotherapy and therefore improved overall survival [25]. Donson et al. noted a 13.7- vs 3.2-month average survival when comparing patients treated with temozolomide for glioblastomas with methylated MGMT promoters compared to those with unmethylated tumors [25]. Interestingly, their results also suggested a survival benefit in the methylated MGMT group independent of treatment, suggesting a possible link between MGMT activity and aggressive tumor behavior [7, 25]. As previously mentioned, the only pediatric glioma group that is likely to harbor MGMT promoter hypermethylation appears to be hemispheric tumors with the H3.3 G34 R/V mutation [11, 13]. The patient presented in this report did not exhibit any epigenetic changes in the MGMT gene.

Hypothesis of symmetry and bilateral presence

The occurrence of gliomas simultaneously in both thalami, sometimes in a symmetric distribution, raises interesting questions regarding the origin and pathophysiology of these tumors. Four hypotheses have been proposed to explain this phenomenon [1]. There first suggests that the tumor originates in one thalamus and spreads to the contralateral thalamus through commissural pathways [1, 27]. Another proposed explanation is that these tumors arise in the subependymal region of the third ventricle and infiltrate bilaterally to affect both thalami independently [7]. Another hypothesis is the cranial extension of a contiguous midbrain tumor (e.g., tectal glioma) following the anatomic mesencephalic tracts [1, 7]. Although each of these hypotheses adequately explain the bilaterality of a tumor, they are less convincing in explaining the symmetrical involvement of bithalamic lesions. The fourth hypothesis that has been proposed is primary bilateral thalamic tumors and an underlying molecular mutation that leads to bilateral lesions [1]. Given the biomolecular differences observed in unilateral thalamic and midline gliomas mentioned earlier, it is possible that bilateral primary thalamic astrocytomas are a unique molecular entity [1]. Furthermore, all prior cases of bilateral thalamic high-grade astrocytomas ($n = 6$) were discovered in male patients (Table 1). The link between hormonal regulation and oncogenesis in symmetric and bilateral tumors remains unclear and requires further investigation, especially in the pediatric population. These observations highlight the significant knowledge gap in understanding the pathophysiology of bilateral pediatric thalamic tumors and affirm the need for further clinical and basic science research.

Prognosis and outcomes

The role of surgical management in the treatment of high-grade bilateral thalamic astrocytomas appears to be limited to biopsy for tissue diagnosis, and treatment of obstructive hydrocephalus [1, 28]. Most pediatric patients diagnosed with high-grade bilateral thalamic astrocytomas receive fractionated radiation and adjuvant chemotherapy without any consensus on a specific regimen (Table 1). Radiation doses typically range from 54 to 59.5 Gy and are administered in daily fractions of 1.8 Gy over 6–7 weeks [29]. Of note, patients under the age of 3 years should not receive post-operative radiotherapy given the deleterious neurocognitive side effects in young children [30]. As for chemotherapy, there have been a variety of different chemotherapeutic regimens utilized in the treatment of pediatric thalamic high-grade gliomas, ranging from older-generation medications such as vincristine and cisplatin to new-generation medications such as temozolomide (alkylating agent) and bevacizumab (vascular endothelial growth factor A inhibitor) [29, 31]. Currently, there is no clear consensus on the optimal treatment regimen, and the combination of temozolomide and bevacizumab is widely administered. However, new clinical data suggests that bevacizumab does not provide any additional therapeutic benefit when compared to temozolomide alone for the treatment of pediatric high-grade gliomas [31].

Prognosis is another critical issue that is frequently challenging for many clinicians, especially when advising anxious parents that are coping with a devastating disease in a loved one. Extrapolating from data available on unilateral thalamic high-grade gliomas in the pediatric population, there appears to be a link between the response to therapy at 8 weeks, and event-free survival/overall survival [29]. Taking this relationship into account, clinicians should consider routine imaging to assess response to therapy at around 8 weeks. Patients with stable disease or partial response to treatment at 8 weeks have a favorable prognosis when compared to those with disease progression in this time interval with 5-year overall survival ranging from 15 to 20% [29].

Our patient received a total radiation dose of 59 Gy over 33 fractions with concurrent temozolomide treatment. Monthly cycles of adjuvant chemotherapy with temozolomide and bevacizumab were administered with excellent tumor response and stability for nearly 1 year (as of writing this report). The patient's most recent radiographic findings are concerning for tumor progression into the left temporal lobe, although radiation-related changes cannot be excluded.

Further characterization of the biomolecular blueprint and development of more effective targeted therapies are critical in treating patients with this rare and malignant tumor.

Exemplary case description

The patient is a 12-year-old boy with medical history of obesity and mastoid cholesteatoma who presented with 4 days of acute onset headaches and nausea. At presentation, there were no focal abnormalities noted by a comprehensive neurological examination. The initial CT of the head demonstrated an ill-defined, heterogeneous, expansile lesion in both thalami. The tumor within the left thalamus was larger with significant mass effect on the third ventricle and foramen Monro leading to severe obstructive hydrocephalus. The MRI of the brain revealed non-enhancing, bilateral masses. Furthermore, the MRI highlighted the obstructive hydrocephalus and entrapment of the left lateral ventricle along with the associated trans-ependymal edema (Fig. 1). Given the severe hydrocephalus, the patient was scheduled for endoscopic biopsy, ventriculoperitoneal (VP) shunt placement, and septum pellucidum fenestration..

Surgery

Using standard endoscopic technique, access to the right lateral ventricle was obtained. Once inside the right lateral ventricle, significant crowding was encountered due to the mass effect from the tumor resulting in bulging of the floor of the lateral ventricle as well as the caudate nucleus. The choroid plexus, thalamo-striate vein, and anterior septal vein were identified to confirm correct positioning. Multiple unsuccessful attempts were made to fenestrate the septum pellucidum, likely thwarted by the mass effect of the tumor and the sharp angle of approach, despite the use of a flexible endoscope. The decision was made to abort the surgery and return the following day with the aid of neuronavigation for a more optimal trajectory to complete the septum pellucidum fenestration. An external ventricular catheter was placed without difficulty and tunneled out through a separate stab incision in the skin. The following day, the patient was taken back to the operating room, and with the aid of neuronavigation, we successfully completed a septum pellucidum fenestration. We then navigated with the endoscope into the contralateral ventricle and confirmed that we had completed an adequate septum pellucidum fenestration. Following the septostomy, a biopsy was taken from the tumor mass through the roof of the third ventricle. At this time, the endoscope was removed and a de novo VP shunt was placed without further complications. Post-operative imaging showed adequate placement of the VP shunt, and no significant post-operative complications.

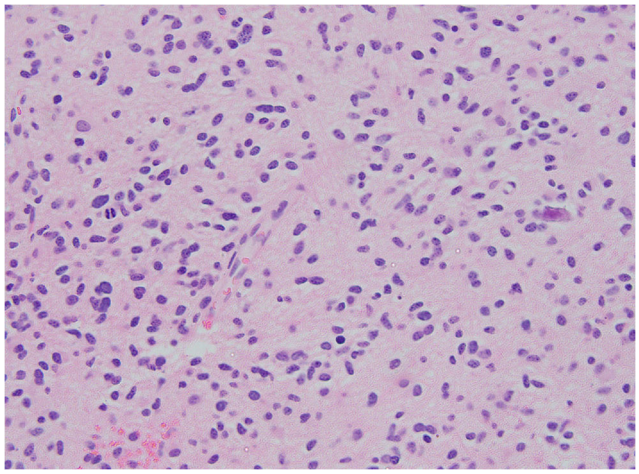

Fig. 2 Hematoxylin and eosin stained section showing pleomorphicastrocytes with hyperchromatic and irregular nuclei without any necrosis or vascular proliferation

Histopathology

Microscopically, the tumor was composed of pleomorphic, atypical astrocytes with hyperchromatic and irregular nuclei embedded in a fibrillary background. There was no necrosis or

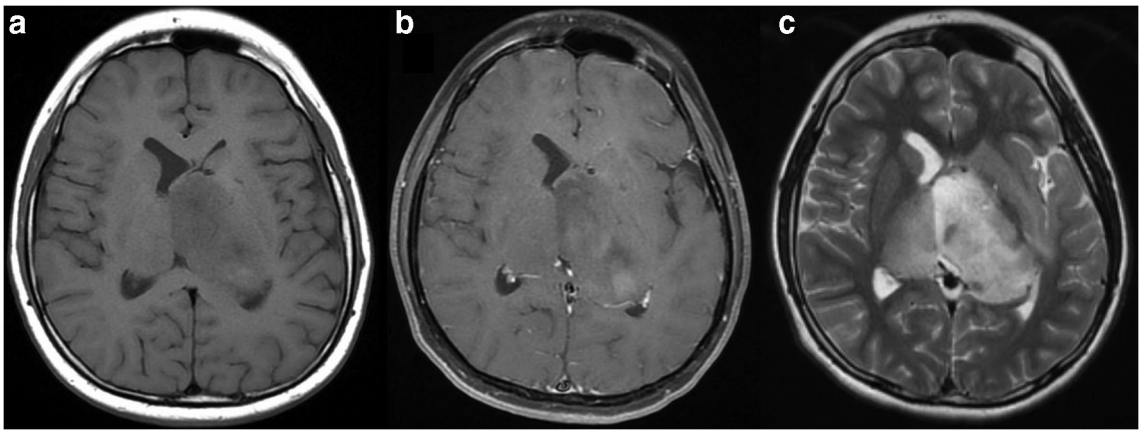

Fig. 1 **a** Pre-operative axial T1-weighted MRI sequence depicting an isointense, asymmetric, and heterogenous mass involving both thalami. **b** Axial T1-weighted post-contrast MRI illustrating asymmetric enlargement of the thalami (left > right), with areas of subtle patchy enhancement. **c** T2-weighted axial MRI sequence demonstrating a heterogeneously hyperintense lesion involving both thalami and causing significant mass effect in the area of frontal horn of the left lateral ventricle and foramen of Monro

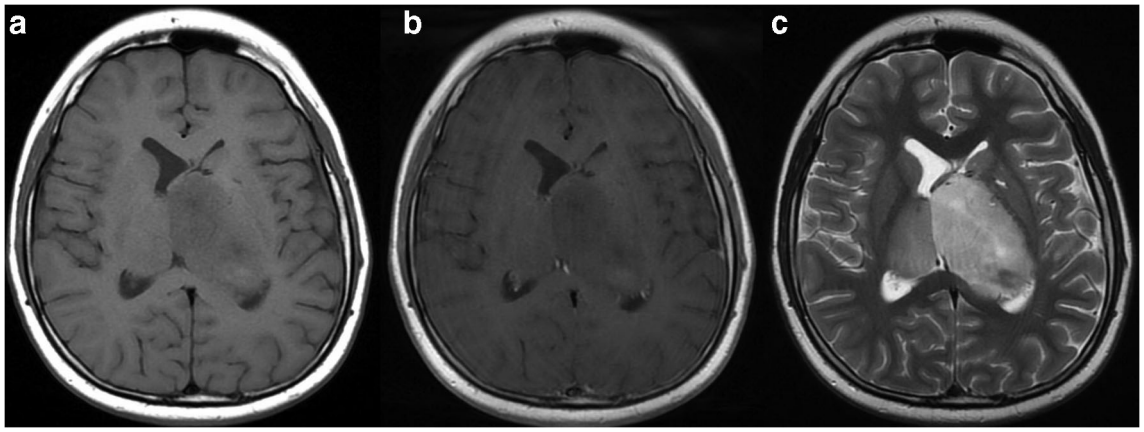

Fig. 3 **a** One-year follow-up axial T1-weighted MRI sequence depicting stable size and signal intensity of the mass involving both thalami along with a VP shunt catheter within the left lateral ventricle. **b** Axial T1-weighted post-contrast MRI illustrating a subtle decrease in the patchy enhancement pattern of the left thalamic mass compared to initial imaging. **c** T2-weighted axial MRI sequence demonstrating stable size of the thalamic lesions with a new area of hypointensity in the posterior margin of the left thalamic lesion

vascular proliferation; however, there were multiple mitotic figures throughout the specimen, with an estimated proliferative activity (Ki-67) of 5–10% (Fig. 2).

Immunohistochemistry and next-generation sequencing (NGS) cancer gene test tumor sequencing performed at the University of California San Francisco identified a frameshift mutation in the TP53 tumor suppressor gene with loss of the remaining wild type allele, a small in-frame insertion/duplication within exon 20 of the EGFR oncogene, and focal homozygous deletion of the CDKN2A and CDKN2B tumor-suppressor genes on chromosome 9p21. The tumor also demonstrated a markedly aneuploid genome, without any pathogenic alterations in IDH1, IDH2, H3F3A, HIST1H3B, BRAF, NF1, FGFR1, MET, or PTEN genes.

Based on the histopathology and molecular profile, this tumor was classified as high-grade astrocytoma, IDH-wild type and histone H3-wildtype, meeting the criteria for WHO grade III.

Treatment and follow up

The patient had no complications immediately post-operatively and was discharged home 2 days after surgery. His treatment regimen consisted of fractionated radiation (59 Gy over 33 fractions) and concomitant temozolomide and bevacizumab for 6 weeks. This was followed by 13 monthly treatment cycles each consisting of 5 days of temozolomide, 2 days of bevacizumab, and the orally administered blood-brain barrier penetrating EGFR pathway inhibitor osimertinib. The thalamic tumors remained stable as followed by serial MRI scans for 11 months, but most recently, there was progression of the T2 signal abnormality into the left temporal stem (Fig. 3). However, the patient has developed no new neurological deficits. We are planning further therapy with re-irradiation, chemotherapy, and nivolumab (anti PD-1 checkpoint inhibitor).

Conclusions

High-grade thalamic astrocytomas affecting both thalami pose a challenge to pediatric neurosurgeons, neuro-oncologists, and neuropathologists given the lack of effective treatment strategies. The role of surgical intervention is limited to biopsy for tissue diagnosis and symptom relief. There is a significant need for further basic science research, and clinical studies to develop effective targeted treatment modalities for this rare disease.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Di Rocco C, Iannelli A (2002) Bilateral thalamic tumors in children. Childs Nerv Syst 18:440–444. https://doi.org/10.1007/s00381-002-0609-9
2. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW (2016) The 2016 World Health Organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 131:803–820. https://doi.org/10.1007/s00401-016-1545-1
3. Cheng Y, Ng HK, Zhang SF, Ding M, Pang JCS, Zheng J, Poon WS (1999) Genetic alterations in pediatric high-grade astrocytomas. Hum Pathol 30:1284–1290
4. Gielen GH, Gessi M, Hammes J, Kramm CM, Waha A, Pietsch T (2013) H3F3A K27M mutation in pediatric CNS tumors: a marker for diffuse high-grade astrocytomas. Am J Clin Pathol 139:345–349. https://doi.org/10.1309/AJCPABOHBC33FVMO
5. Rizzo D, Ruggiero A, Martini M, Rizzo V, Maurizi P, Riccardi R (2015) Molecular biology in pediatric high-grade glioma: impact on prognosis and treatment. Biomed Res Int 2015:215135–215110. https://doi.org/10.1155/2015/215135

6. Cinalli G, Aguirre DT, Mirone G, Ruggiero C, Cascone D, Quaglietta L, Aliberti F, Santi S', Buonocore MC, Nastro A, Spennato P (2018) Surgical treatment of thalamic tumors in children. J Neurosurg Pediatr 21:247–257. https://doi.org/10.3171/2017.7.Peds16463
7. Esteve F et al (1999) MR spectroscopy of bilateral thalamic gliomas. AJNR Am J Neuroradiol 20:876–881
8. Gupta A, Shaller N, McFadden KA (2017) Pediatric thalamic gliomas: an updated review. Arch Pathol Lab Med 141:1316–1323. https://doi.org/10.5858/arpa.2017-0249-RA
9. Schwartzentruber J, Korshunov A, Liu XY, Jones DTW, Pfaff E, Jacob K, Sturm D, Fontebasso AM, Quang DAK, Tönjes M, Hovestadt V, Albrecht S, Kool M, Nantel A, Konermann C, Lindroth A, Jäger N, Rausch T, Ryzhova M, Korbel JO, Hielscher T, Hauser P, Garami M, Klekner A, Bognar L, Ebinger M, Schuhmann MU, Scheurlen W, Pekrun A, Frühwald MC, Roggendorf W, Kramm C, Dürken M, Atkinson J, Lepage P, Montpetit A, Zakrzewska M, Zakrzewski K, Liberski PP, Dong Z, Siegel P, Kulozik AE, Zapatka M, Guha A, Malkin D, Felsberg J, Reifenberger G, von Deimling A, Ichimura K, Collins VP, Witt H, Milde T, Witt O, Zhang C, Castelo-Branco P, Lichter P, Faury D, Tabori U, Plass C, Majewski J, Pfister SM, Jabado N (2012) Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature 482:226–231. https://doi.org/10.1038/nature10833
10. Wu G, Broniscer A, McEachron T, Lu C, Paugh BS, Becksfort J, Qu C, Ding L, Huether R, Parker M, Zhang J, Gajjar A, Dyer MA, Mullighan CG, Gilbertson RJ, Mardis ER, Wilson RK, Downing JR, Ellison DW, Zhang J, Baker SJ, St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project (2012) Somatic histone H3 alterations in pediatric diffuse intrinsic pontine gliomas and non-brainstem glioblastomas. Nat Genet 44:251–253. https://doi.org/10.1038/ng.1102
11. Mackay A et al (2017) Integrated molecular meta-analysis of 1,000 pediatric high-grade and diffuse intrinsic pontine glioma. Cancer Cell 32:520–537 e525. https://doi.org/10.1016/j.ccell.2017.08.017
12. Broniscer A, Hwang SN, Chamdine O, Lin T, Pounds S, Onar-Thomas A, Chi L, Shurtleff S, Allen S, Gajjar A, Northcott P, Orr BA (2018) Bithalamic gliomas may be molecularly distinct from their unilateral high-grade counterparts. Brain Pathol 28:112–120. https://doi.org/10.1111/bpa.12484
13. Korshunov A, Schrimpf D, Ryzhova M, Sturm D, Chavez L, Hovestadt V, Sharma T, Habel A, Burford A, Jones C, Zheludkova O, Kumirova E, Kramm CM, Golanov A, Capper D, von Deimling A, Pfister SM, Jones DTW (2017) H3-/IDH-wild type pediatric glioblastoma is comprised of molecularly and prognostically distinct subtypes with associated oncogenic drivers. Acta Neuropathol 134:507–516. https://doi.org/10.1007/s00401-017-1710-1
14. Castel D, Philippe C, Calmon R, le Dret L, Truffaux N, Boddaert N, Pagès M, Taylor KR, Saulnier P, Lacroix L, Mackay A, Jones C, Sainte-Rose C, Blauwblomme T, Andreiuolo F, Puget S, Grill J, Varlet P, Debily MA (2015) Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. Acta Neuropathol 130:815–827. https://doi.org/10.1007/s00401-015-1478-0
15. Abedalthagafi M, Phillips JJ, Kim GE, Mueller S, Haas-Kogen DA, Marshall RE, Croul SE, Santi MR, Cheng J, Zhou S, Sullivan LM, Martinez-Lage M, Judkins AR, Perry A (2013) The alternative lengthening of telomere phenotype is significantly associated with loss of ATRX expression in high-grade pediatric and adult astrocytomas: a multi-institutional study of 214 astrocytomas. Mod Pathol 26:1425–1432. https://doi.org/10.1038/modpathol.2013.90
16. Wiestler B, Capper D, Holland-Letz T, Korshunov A, von Deimling A, Pfister SM, Platten M, Weller M, Wick W (2013) ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis. Acta Neuropathol 126:443–451. https://doi.org/10.1007/s00401-013-1156-z
17. Durant ST (2012) Telomerase-independent paths to immortality in predictable cancer subtypes. J Cancer 3:67–82. https://doi.org/10.7150/jca.3965
18. Nguyen DN, Heaphy CM, de Wilde RF, Orr BA, Odia Y, Eberhart CG, Meeker AK, Rodriguez FJ (2013) Molecular and morphologic correlates of the alternative lengthening of telomeres phenotype in high-grade astrocytomas. Brain Pathol 23:237–243. https://doi.org/10.1111/j.1750-3639.2012.00630.x
19. Andrae J, Gallini R, Betsholtz C (2008) Role of platelet-derived growth factors in physiology and medicine. Genes Dev 22:1276–1312. https://doi.org/10.1101/gad.1653708
20. Paugh BS, Zhu X, Qu C, Endersby R, Diaz AK, Zhang J, Bax DA, Carvalho D, Reis RM, Onar-Thomas A, Broniscer A, Wetmore C, Zhang J, Jones C, Ellison DW, Baker SJ (2013) Novel oncogenic PDGFRA mutations in pediatric high-grade gliomas. Cancer Res 73:6219–6229. https://doi.org/10.1158/0008-5472.CAN-13-1491
21. Wu G, Diaz AK, Paugh BS, Rankin SL, Ju B, Li Y, Zhu X, Qu C, Chen X, Zhang J, Easton J, Edmonson M, Ma X, Lu C, Nagahawatte P, Hedlund E, Rusch M, Pounds S, Lin T, Onar-Thomas A, Huether R, Kriwacki R, Parker M, Gupta P, Becksfort J, Wei L, Mulder HL, Boggs K, Vadodaria B, Yergeau D, Russell JC, Ochoa K, Fulton RS, Fulton LL, Jones C, Boop FA, Broniscer A, Wetmore C, Gajjar A, Ding L, Mardis ER, Wilson RK, Taylor MR, Downing JR, Ellison DW, Zhang J, Baker SJ (2014) The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat Genet 46:444–450. https://doi.org/10.1038/ng.2938
22. Koschmann C et al (2016) Characterizing and targeting PDGFRA alterations in pediatric high-grade glioma. Oncotarget 7:65696–65706. https://doi.org/10.18632/oncotarget.11602
23. Parrales A, Iwakuma T (2015) Targeting oncogenic mutant p53 for cancer therapy. Front Oncol 5:288. https://doi.org/10.3389/fonc.2015.00288
24. Pollack IF, Finkelstein SD, Woods J, Burnham J, Holmes EJ, Hamilton RL, Yates AJ, Boyett JM, Finlay JL, Sposto R (2002) Expression of p53 and prognosis in children with malignant gliomas. N Engl J Med 346:420–427. https://doi.org/10.1056/NEJMoa012224
25. Donson AM, Addo-Yobo SO, Handler MH, Gore L, Foreman NK (2007) MGMT promoter methylation correlates with survival benefit and sensitivity to temozolomide in pediatric glioblastoma. Pediatr Blood Cancer 48:403–407. https://doi.org/10.1002/pbc.20803
26. Srivastava A, Jain A, Jha P, Suri V, Sharma MC, Mallick S, Puri T, Gupta DK, Gupta A, Sarkar C (2010) MGMT gene promoter methylation in pediatric glioblastomas. Childs Nerv Syst 26:1613–1618. https://doi.org/10.1007/s00381-010-1214-y
27. Carter DJ, Wiedmeyer DA, Antuono PG, Ho KC (1989) Correlation of computed tomography and postmortem findings of a diffuse astrocytoma: a case report. Comput Med Imaging Graph 13:491–494
28. Bilginer B, Narin F, Işıkay I, Oguz KK, Söylemezoglu F, Akalan N (2014) Thalamic tumors in children. Childs Nerv Syst 30:1493–1498. https://doi.org/10.1007/s00381-014-2420-9
29. Kramm CM, Butenhoff S, Rausche U, Warmuth-Metz M, Kortmann RD, Pietsch T, Gnekow A, Jorch N, Janssen G, Berthold F, Wolff JE (2011) Thalamic high-grade gliomas in children: a distinct clinical subset? Neuro-Oncology 13:680–689. https://doi.org/10.1093/neuonc/nor045
30. Kann BH, Park HS, Lester-Coll NH, Yeboa DN, Benitez V, Khan AJ, Bindra RS, Marks AM, Roberts KB (2016) Postoperative radiotherapy patterns of care and survival implications for medulloblastoma in young children. JAMA Oncol 2:1574–1581. https://doi.org/10.1001/jamaoncol.2016.2547

31. Grill J, Massimino M, Bouffet E, Azizi AA, McCowage G, Cañete A, Saran F, le Deley MC, Varlet P, Morgan PS, Jaspan T, Jones C, Giangaspero F, Smith H, Garcia J, Elze MC, Rousseau RF, Abrey L, Hargrave D, Vassal G (2018) Phase II, open-label, randomized, multicenter trial (HERBY) of bevacizumab in pediatric patients with newly diagnosed high-grade glioma. J Clin Oncol 36:951–958. https://doi.org/10.1200/JCO.2017.76.0611