CASE REPORT

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Initially disseminated pediatric high-grade midline glioma without H3 K27M alteration – a case report and literature review

Inicijalno diseminovani pedijatrijski visokogradusni gliom srednje linije bez H3 K27M alteracije – prikaz bolesnika i pregled literature

Dragana Stanić Tišma*†, Danica Grujičić†‡, Aleksandar Kostić‡, Marija Denčić Fekete†, Predrag Filipović*, Marija Popović-Vuković*†, Jelena Bokun*†, Marina Nikitović*†

***Institute of Oncology and Radiology of Serbia, Belgrade, Serbia; †University of Belgrade, Faculty of Medicine, Belgrade, Serbia; ‡University Clinical Center of Serbia, Clinic for Neurosurgery, Belgrade, Serbia**

Abstract

Introduction. Pediatric high-grade gliomas (HGGs) constitute an extremely heterogeneous group of highly aggressive brain tumors. While leptomeningeal dissemination is commonly observed in patients through the course of the disease, cases with initial dissemination are rare. **Case report.** This paper reports the case of a 12-year-old boy diagnosed with an initially disseminated HGGs with midline localization. Despite surgical intervention and a multidisciplinary treatment approach involving craniospinal radiotherapy and chemotherapy, the patient experienced rapid neurological deterioration and disease progression, and ultimately succumbed to the disease 13 months after diagnosis. In contrast to the vast majority of similar pediatric cases documented in the literature, our patient exhibited an absence of H3 K27M alteration. To our knowledge, this is a unique presentation of a midline HGG with leptomeningeal cranial and spinal dissemination at diagnosis without the expected molecular pattern typically associated with such cases. **Conclusion.** This case highlights that, whether disseminated or not, pediatric HGGs have similarly poor survival outcomes with no effective treatments. It also underscores the widespread challenge of incomplete molecular profiling in these tumors. This emphasizes the urgent need for a comprehensive molecular analysis of these tumors worldwide to advance diagnosis and guide the development of personalized therapy.

Key words:
brain neoplasms; glioma; neoplasm metastasis; pediatrics; survival.

Apstrakt

Uvod. Pedijatrijski gliomi visokog gradusa (*high-grade gliomas* – HGG) čine izuzetno heterogenu grupu visoko agresivnih tumora mozga. Dok se leptomeningealna diseminacija obično opaža kod bolesnika tokom bolesti, slučajevi sa inicijalnom diseminacijom su retki. **Prikaz bolesnika.** Pririkazan je slučaj 12-godišnjeg dečaka sa dijagnozom inicijalno diseminovanog HGG srednje lokalizacije. Uprkos hirurškoj intervenciji i multidisciplinarnom pristupu lečenja koji je uključivao kraniospinalnu radioterapiju i hemioterapiju, bolesnik je doživeo brzo neurološko pogoršanje i progresiju bolesti i na kraju je podlegao bolesti 13 meseci nakon dijagnoze. Za razliku od velike većine sličnih pedijatrijskih slučajeva dokumentovanih u literaturi, naš bolesnik je pokazao odsustvo H3 K27M alteracije. Prema našim saznanjima, ovo je jedinstvena prezentacija HGG srednje lokalizacije sa leptomeningealnom kranijalnom i spinalnom diseminacijom pri postavljanju dijagnoze bez očekivanog molekularnog obrasca koji je tipično povezan s takvim slučajevima. **Zaključak.** Ovim prikazom slučaja ističe se da su ishodi preživljavanja pedijatrijskih bolesnika sa HGG, bez obzira da li su diseminovani ili ne, podjednako loši, uz odsustvo efikasnih terapijskih opcija. Takođe, ukazuje na veliki problem nepotpune molekularne karakterizacije ovih tumora. Ovi podaci dodatno naglašavaju hitnu potrebu sveobuhvatne molekularne analize ovih tumora širom sveta, u cilju unapređenja dijagnostike i razvoja personalizovanih terapijskih pristupa.

Ključne reči:
mozak, neoplazme; gliom; neoplazme, metastaze; pedijatrija; preživljavanje.

Correspondence to: Dragana Stanić Tišma, Institute of Oncology and Radiology of Serbia, Pasterova 14, Belgrade, Serbia. E-mail: dragana221@gmail.com, dragana.stanic@ncrc.ac.rs

Introduction

Pediatric high-grade gliomas (HGGs) constitute up to 20% of pediatric tumors of the central nervous system (CNS) [1]. These tumors' propensity for rapid progression complicates their management, resulting in an unfavorable prognosis. HGGs remain the leading cause of pediatric brain tumor death. The current standard of care is maximal resection of the tumor, followed by radiochemotherapy. Surgical resection, whenever feasible, provides the most significant overall survival (OS) benefit [2].

Pediatric HGGs are an extremely heterogeneous group of highly aggressive brain tumors. After years of molecular and clinical research, H3 K27M-altered diffuse midline glioma, H3 G34-mutant diffuse hemispheric glioma, and diffuse pediatric-type HGG, H3-wildtype and IDH-wildtype, became distinct entities of the pediatric HGG group in the new 5th edition of the World Health Organization (WHO) 2021 CNS tumor classification [3].

Diffuse midline gliomas (DMGs) can arise from midline structures, such as the brainstem, cerebellum and cerebellar peduncles, thalamus, hypothalamus, pineal region, spinal cord, third ventricle, and the ganglio-capsular region. The majority, around 70–80% of pediatric DMGs, possess a lysine-to-methionine mutation at position 27 of histone 3.1, 3.2, or 3.3, which forms a pathological histone mutation that causes derepression of polycomb repressive complex 2 (PRC2) [4]. PRC2 is an enzyme complex that maintains gene transcriptional repression and plays an essential role in the maintenance of cellular identity as well as normal organismal development [5]. These molecular changes partly determine the intrinsic nature of the tumor, its invasive growth, and its unresponsiveness to systemic therapy (which is also caused by the blood-brain barrier). Considering all of the above, patients with H3 K27M-altered DMGs have a rather dismal prognosis despite the advances in therapy, with a two-year survival of less than 10% [6]. The survival of patients with H3 G34-mutant diffuse hemispheric glioma and diffuse pediatric-type HGG (H3-wildtype and IDH-wildtype) is slightly better than that of H3 K27-altered tumors. However, overall prognosis unfortunately remains poor, with two-year OS rates of approximately 20–30% for the former and 15–25% for the latter [7–8].

The current standard treatment for DMGs is focal radiotherapy, which may provide temporary symptom relief and radiographic stabilization but does not significantly alter the disease's poor prognosis. Although various systemic agents and targeted therapies are under investigation, none have yet demonstrated a proven benefit in improving outcomes [9].

DMGs (especially pontine gliomas) are known to metastasize along the neuraxis [10–12]. In literature, leptomeningeal dissemination occurred in 17–56% of patients prior to their death [13–15]. However, at the time of diagnosis, leptomeningeal dissemination is rare, with reported incidence rates ranging from 3% to 18% [15, 16]. Extraneural metastases from DMGs are very rare, typically localized in the bones, and are usually observed after surgical interventions, which are thought to disrupt the blood-brain barrier [17, 18]. Furthermore, in some cases, dissemination to the peritoneal cavity *via* shunt was observed [19]. Most data on DMG dissemination patterns come from isolated case reports or small series, with no large-scale systematic studies on dissemination across specific molecular subtypes. The majority of tumors described in the literature with dissemination and aggressive behavior, whether metastasizing within or outside the CNS, are associated with the H3 K27M mutation [18–22]. Since initially disseminated DMGs are exceptionally rare, there are no consensus guidelines for treatment.

The national referral centers for treating childhood brain tumors in Serbia are the University Clinical Center of Serbia, Clinic for Neurosurgery, Belgrade, Serbia, and the Institute of Oncology and Radiology of Serbia, Belgrade. These hospitals admit any pediatric patient suspected of having a brain tumor to confirm the diagnosis and devise a treatment strategy through a common multidisciplinary team. A case of a child was presented with initially disseminated HGG with midline localization, without H3 K27M alteration.

Case report

A 12-year-old boy presented to the local pediatrician with vertigo and instability while walking. According to the parents, the symptoms had manifested several days prior to admission. Neurological examination revealed discrete divergent strabismus. Nystagmus was present during gaze to the left. Romberg's test, as well as the tandem gait test, was positive. The rest of the examination was uneventful.

Initially, a head computed tomography (CT) was performed and revealed multiple tumor lesions in the brain, an expansive lesion in the middle portion of the left cerebellar hemisphere, the entire pons expanded, measuring 30 mm in its anterior-posterior diameter and cerebellar tonsils descending 5 mm below the foramen magnum, and another lesion in the area of the anterior genus of the corpus callosum that spread contralaterally for about 5 mm (Figure 1).

The patient underwent neurosurgical intervention in the following days. Maximal reduction of the tumor in the posterior cranial *fossa* was performed. The postoperative recovery period was without any complications.

Histopathology revealed a high-grade glial tumor, composed of poorly differentiated astrocytes (Figure 2).

Immunohistochemically (IHC), tumor cells variably expressed INI1, S-100, GFAP, OLIG2, CD56, synaptophysin, MAP2, and p35. H3K27me3 staining showed mostly retained nuclear expression, while epithelial membrane antigen (EMA) and IDH1 p.R132H were negative. ATRX was deemed inconclusive due to inconsistent staining and the absence of a positive internal control. A high proliferation rate was confirmed with the Ki-67 proliferation index, focally approaching 30% (Figure 3). Real-time polymerase chain reaction for the *BRAF* gene mutation did not show any presence. In summary, the diagnosis of pediatric HGG, not otherwise specified, was made by our experienced neuropathologist, with a remark

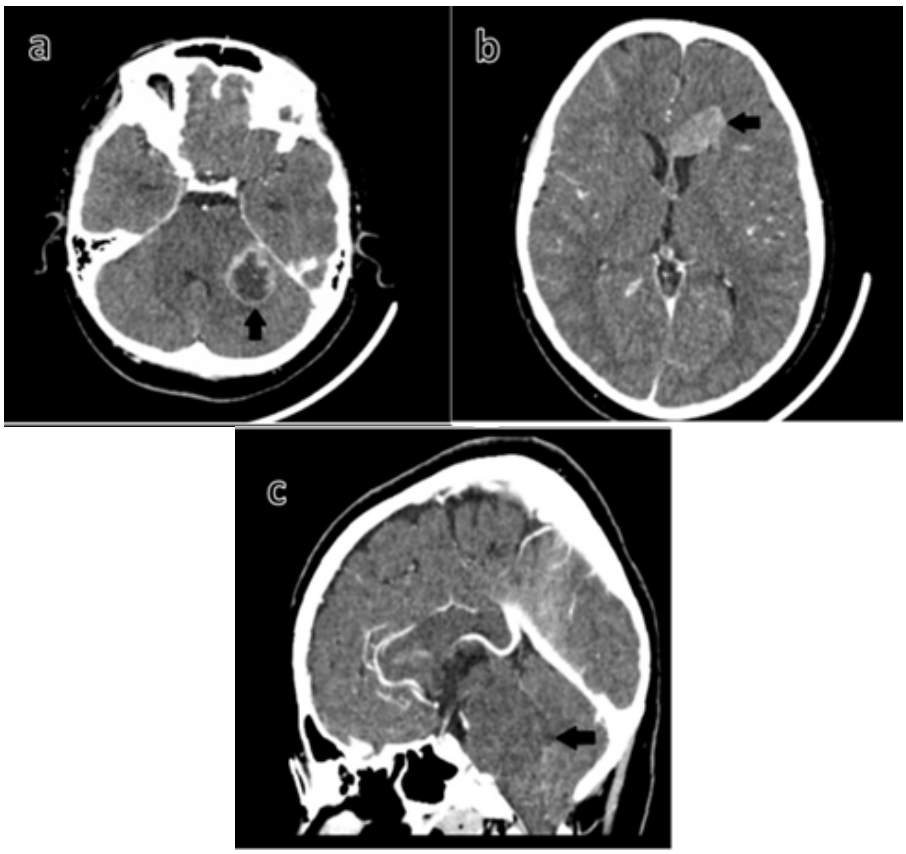

Fig. 1 – Initial computed tomography imaging. a) An expansive heterogeneous lesion with ring postcontrast enhancement in the middle level of the left cerebellar hemisphere. The lesion infiltrates the left cerebellar peduncle (black arrow). b) A hyperdense lesion with irregular edges and postcontrast enhancement at the level of the genus/anterior portion of the left corpus callosum (black arrow). c) The pons exhibits significant expansion (black arrow).

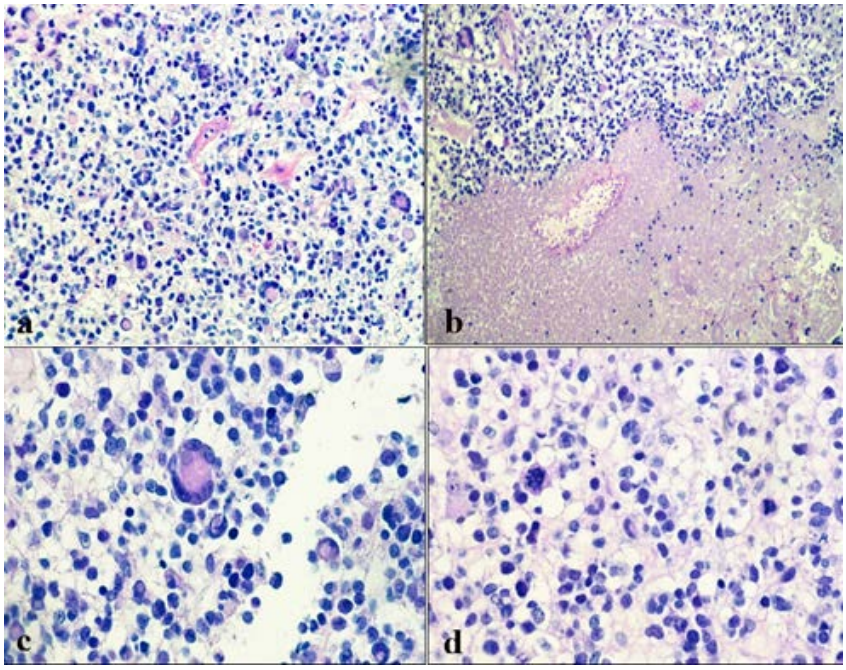

Fig. 2 – High-grade diffuse pediatric glioma, not otherwise specified (hematoxylin and eosin staining). a) Hypercellular tumor composed of pleomorphic glial cells with hyperchromatic nuclei and indistinct nucleoli (×10). b) Foci of non-palisading necrosis (×10). c) Multinuclear giant tumor cell within a sheet of smaller cells (×20). d) Conspicuous mitotic activity with atypical mitosis (×20).

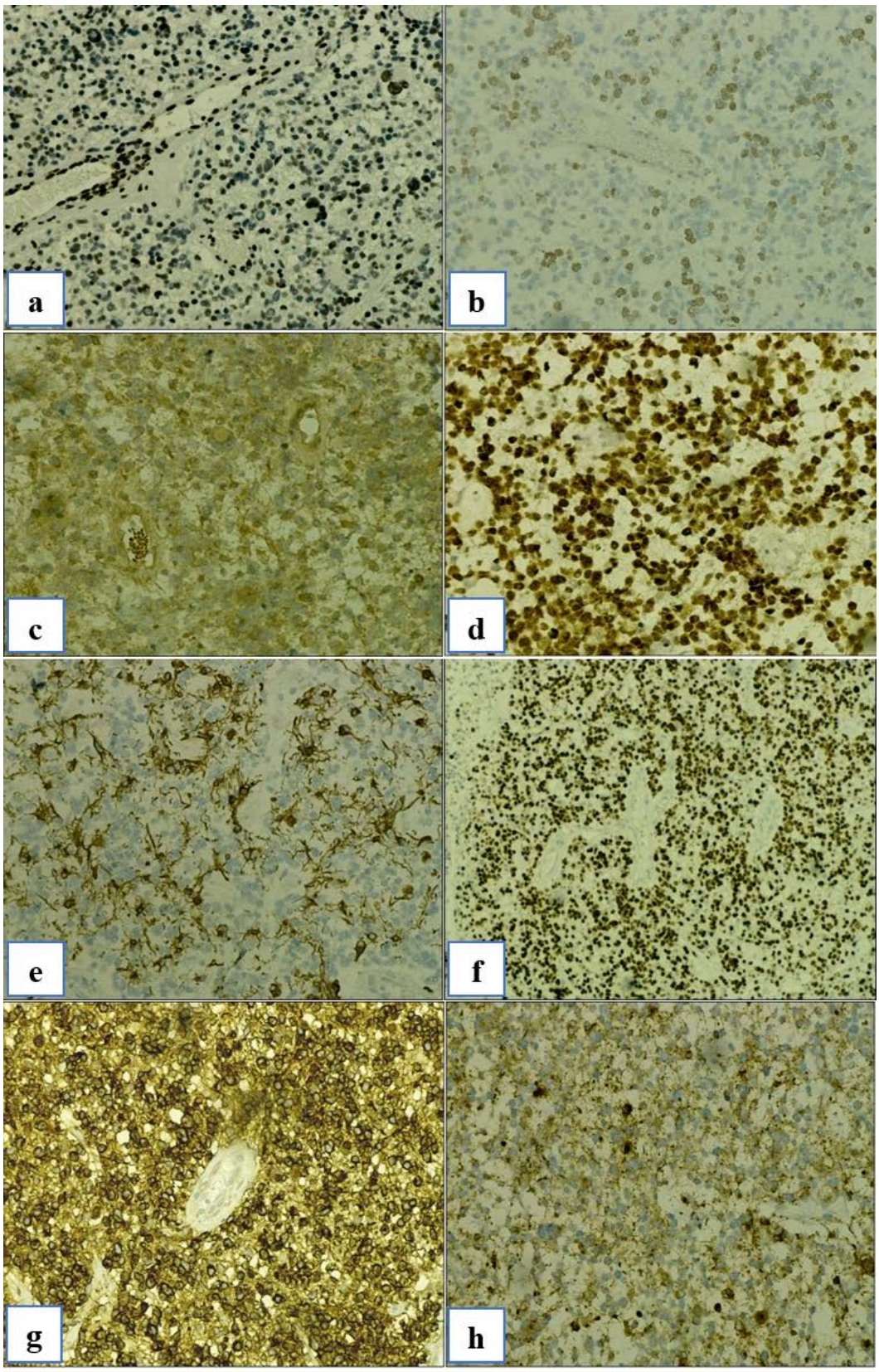

Fig. 3 – High-grade diffuse pediatric glioma, not otherwise specified (immunohistochemical studies): a) focal GFAP immunoreactivity; b) diffuse OLIG2 immunoreactivity; c) IDH1 immunonegativity; d) diffuse p53 immunoexpression; e) H3K27me3 mostly retained nuclear expression, giant multinucleated tumor cells with retained nuclear expression; f) high Ki-67 proliferation index; g) diffuse MAP2 immunoexpression; h) synaptophysin staining in rare tumor cells.

***Note*: All images were captured at ×20 magnification, except f), which was at ×10.**

that further molecular analysis should be done in order to closely define this tumor entity.

The patient was presented to the multidisciplinary tumor board, which indicated treatment continuation with radiotherapy and chemotherapy with temozolomide, according to the HGG protocols. Given the absence of consensus guidelines for disseminated cases, we based our decision on the best available evidence and clinical judgment.

Shortly after the tumor board presentation, the patient's condition deteriorated with the development of dysphagia, dysarthria, and headaches. Neurological examination demonstrated hemiparesis on the left side as well as the presence of bulbar symptomatology. At this time, the child could not walk.

Due to the neurological deterioration, magnetic resonance imaging (MRI) of the head and entire spine was performed. This MRI, performed three weeks after the surgery, showed significant growth of the left frontal lesion with a contralateral propagation and signs of perifocal edema. Diffuse tumor infiltration of the pons was also present, appearing T2 hyperintense. In addition, a smaller lesion was visible on the T1 post-contrast images within the postoperative cavity in the left cerebellar hemisphere, with residual tumor adherent to the cavity wall. The tumor lesions showed an elevation of perfusion as well as a restriction of diffusion. The findings from the spine imaging strongly indicated the presence of leptomeningeal dissemination (three nodules/drop metastases were revealed at the level of the 10^{th} and 11^{th} thoracic vertebral bodies – Th10 and Th11) (Figure 4).

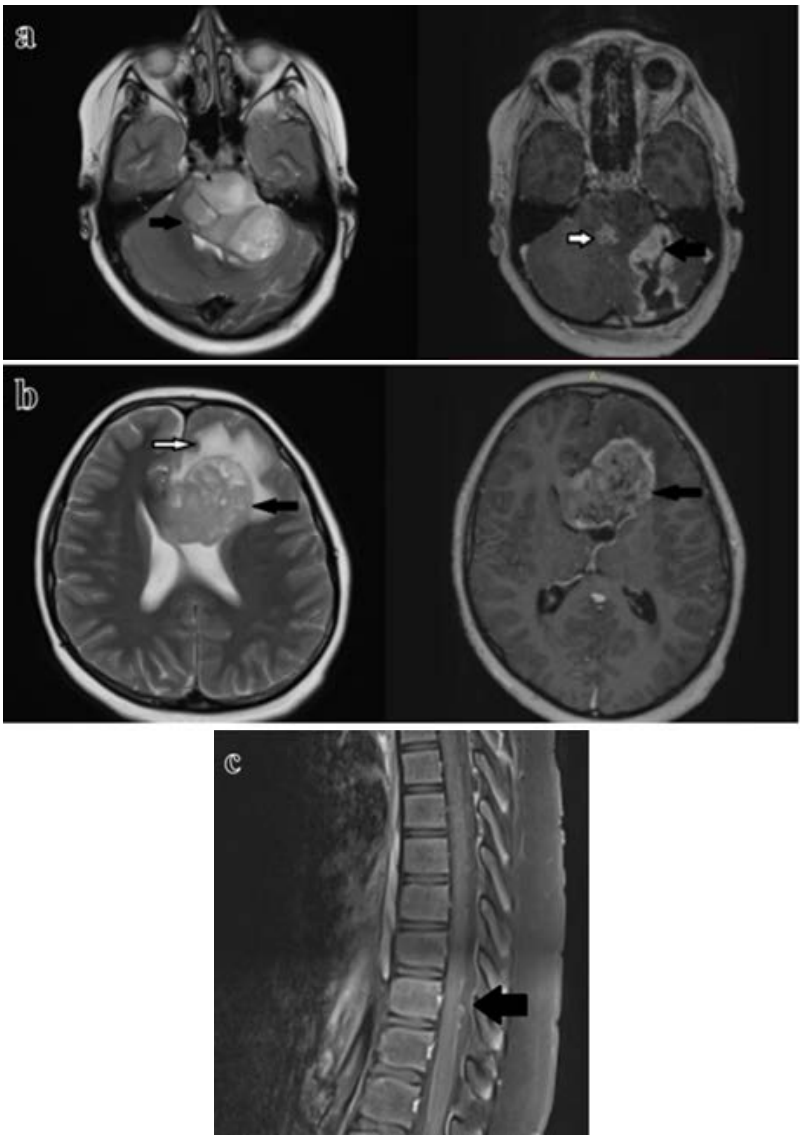

Fig. 4 – Postoperative brain and spine magnetic resonance imaging. a) A postoperative cavity with the presence of a residual tumor that is adherent to the cavity wall (black arrow, right). Diffuse infiltration of the pons (black arrow, left) with a demarked T1 postcontrast lesion (white arrow, right). b) Significant progression of the frontal lesion (black arrows, left and right) with contralateral propagation and infiltration of the anterior portion of the corpus callosum (white arrow, left). c) On T1 postcontrast images, three nodules at the level of Th10 and Th11 vertebral bodies are highly suspicious for leptomeningeal dissemination (black arrow).

Radiotherapy was initiated with concomitant chemotherapy using temozolomide (75 mg/m^2 daily). The patient was planned for craniospinal irradiation with 36 Gy in 20 fractions, followed by a sequential boost of 18 Gy in 10 fractions to the intracranial areas of the disease (the frontal lesion and posterior cranial *fossa*), for a total dose of 54 Gy. After five fractions, the treatment was complicated by grade 2 neutropenia (according to the Common Terminology Criteria for Adverse Events v.5.0), which required granulocyte-colony stimulating factor administration, and grade 2 thrombocytopenia, which required platelet transfusion. Due to hematological toxicity, concomitant temozolomide was discontinued. Radiotherapy was completed without interruptions.

Evaluation of the disease was performed six weeks after. MRI of the head and spine revealed volumetric regression of the tumor lesion located frontally, while other intracranial lesions were stationary. Regarding spinal dissemination, a new nodule, with postcontrast enhancement, appeared at the level of Th4 (Figure 5).

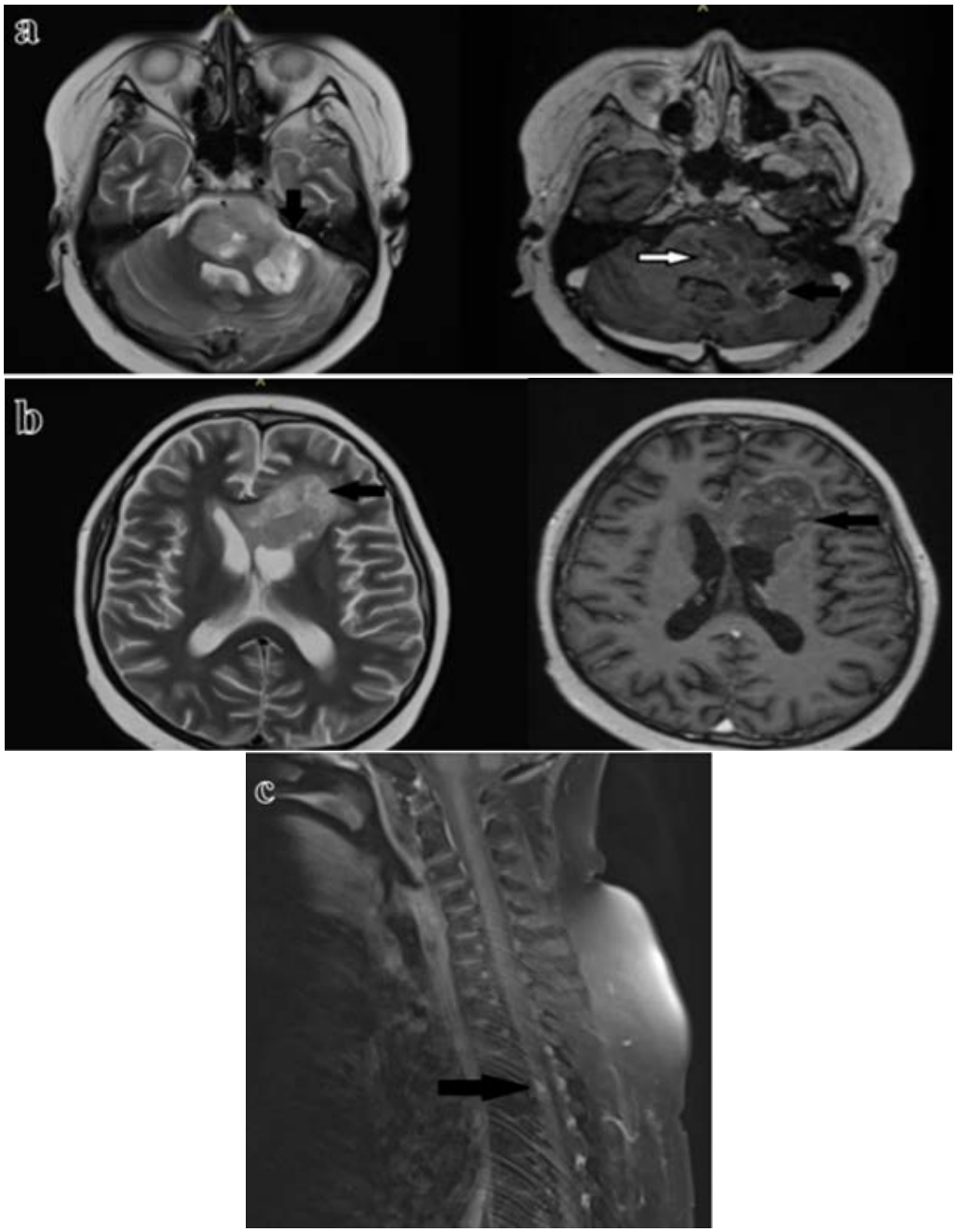

Fig. 5 – Brain and spine magnetic resonance imaging 6 weeks after radiotherapy. a) Retracted postoperative cavity with a still present postcontrast enhancement of the cavity wall (black arrow, right). Diffuse tumor infiltration within the pons persists (black arrow, left) with a similar postcontrast-enhanced lesion diameter (white arrow, right). b) A frontal lesion with still persistent contralateral spread with volumetric regression (black arrows, left and right). c) A new postcontrast-enhanced nodule appeared at the level of the Th4 vertebral body (black arrow).

Treatment was continued with adjuvant monthly temozolomide (200 mg/m^2 daily on days 1–5 of each 28-day cycle). The neurological status of the patient deteriorated. He developed paraplegia and was completely bedridden with episodes of vomiting and headaches. After four cycles of adjuvant temozolomide, MRI of the head and spine demonstrated further volumetric regression of the frontal lesion, but a small new lesion appeared caudally, while the lesions in the posterior *fossa* and spine were unchanged.

Adjuvant treatment was continued for up to eight cycles of adjuvant temozolomide. During this period, the patient occasionally developed grade 3 neutropenia, which required administration of granulocyte-colony stimulating factor. MRI evaluation showed significant progression of the intracranial disease: the frontal lesion expanded in all directions, the pontine lesion also progressed, and the dominant progression was downward to the medulla oblongata (Figure 6). Radiologic progression was followed by further neurological deterioration, including somnolence, immobility, and dyspnea. The patient died 13 months after the diagnosis.

Discussion

Over a 16-year period, from January 2007 to December 2022, 58 patients aged 0–18 years with newly diagnosed HGGs and 37 with diffuse intrinsic pontine gliomas (DIPG) were treated at the Institute of Oncology and Radiology of Serbia. Of these, 11 (11.6%) patients developed metastases. In 10 (10.5%) patients, metastases occurred after initial treatment, while in 1 (1.1%) patient metastases were present at diagnosis – the case described here.

To support the analysis and contextualization of this case, we performed a focused narrative literature review. The search was conducted using PubMed and Google Scholar, employing keywords such as “pediatric high-grade glioma,” “diffuse midline glioma,” “H3K27M,” “H3-wildtype,” “leptomeningeal dissemination,” and “CNS metastases.” Studies included were English language publications involving pediatric patients, with a focus on case reports, retrospective series, and review articles published up to December 2024. Priority was given to literature describing

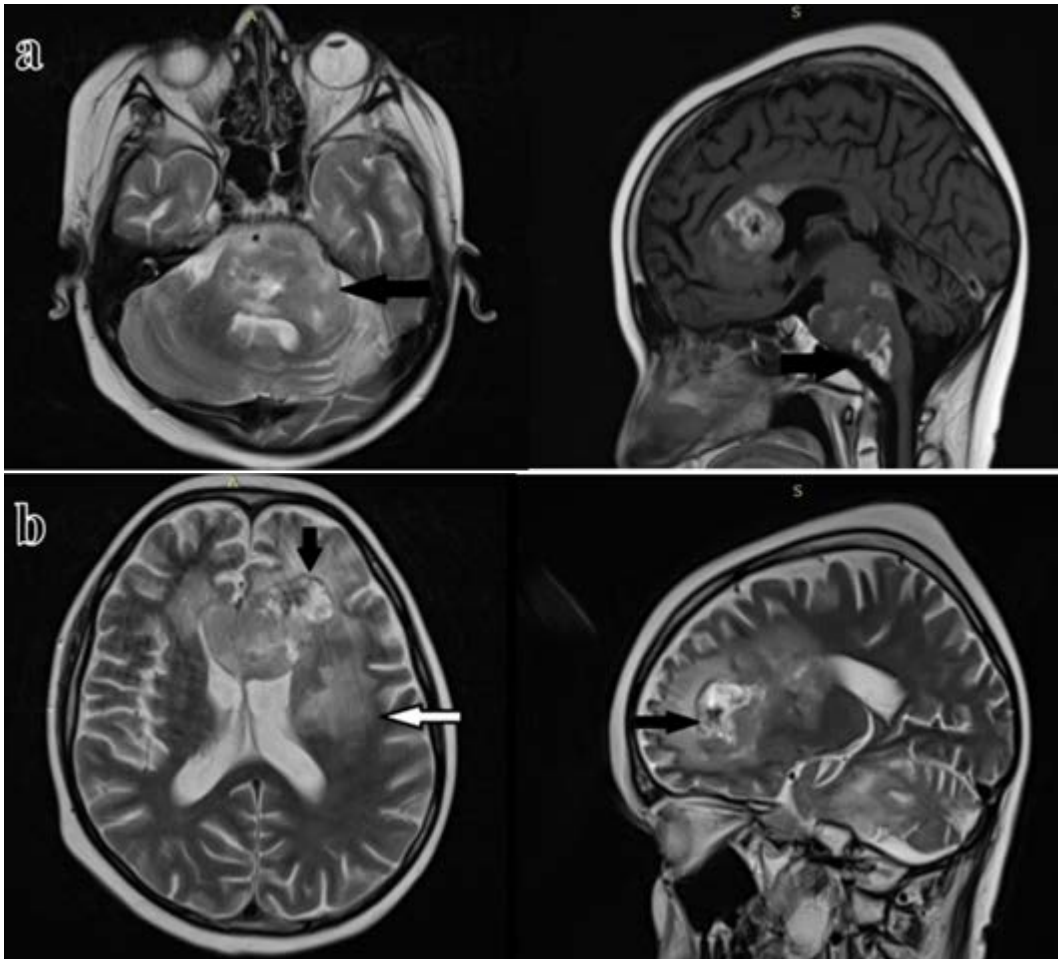

Fig. 6 – Brain magnetic resonance imaging after 8 cycles of adjuvant temozolomide. a) A marked progression of pontine infiltration in all directions (black arrow, left), but the dominant is caudal into the medulla oblongata (black arrow, right). b) Lesion localized frontally in marked progression with infiltration of the rostrum, anterior portion of the corpus callosum (black arrow, left), left corona radiata, and centrum semiovale (white arrow, left) with marked perifocal edema (black arrow, right).

disseminated DMG cases, their molecular characteristics, diagnostic approaches, and treatment outcomes. This review aimed to highlight patterns of dissemination, clinical management strategies, and prognostic differences relevant to our case.

In the largest series so far, the German group reported a 3.1% incidence of primary [16] and 17% of secondary dissemination [14] in patients with HGGs and DIPG included in the HIT-GBM studies. We found a lower incidence of primary and secondary tumor dissemination in our patients, most probably due to the low frequency of completely performed CNS staging initially and during follow-up. The MRI of the brain was conducted routinely in most of our patients, but the MRI of the spine, as well as cerebrospinal fluid cytology, were not a part of the examination in patients with HGGs and DIPG until recent years, so there is a high possibility that some cases with dissemination were not diagnosed initially and subsequently during the course of the disease. In a study by Sethi et al. [15], a high incidence of leptomeningeal dissemination was detected in their cohort of pediatric DIPG patients with close prospective neuraxis MRI surveillance (56% of patients, 18.7% initially). They also found dissemination in two of their patients on autopsy, without previous detection on imaging. Buczkowicz et al. [23] discovered that 38.6% of the patients with DIPG had leptomeningeal spread at autopsy. Recognizing the high potential for leptomeningeal dissemination in HGGs with midline localization, we have successfully integrated routine craniospinal MRI into standard protocols in Serbia for both initial diagnosis and follow-up examinations in pediatric patients with these tumors and all HGGs. Whenever possible, we additionally perform a cytological examination of cerebrospinal fluid.

In the past, surgical intervention for DIPG was primarily focused on treating hydrocephalus, and biopsies were uncommon due to the tumor's location. However, in the current molecular era, obtaining a definitive pathological diagnosis of pediatric HGGs and identifying molecular targets has become increasingly important for research and treatment planning. Biopsies, although limited in their prognostic yield, are necessary for accurate diagnosis. In a case described by Navarro et al. [24], a dural biopsy targeting the lumbar region provided a diagnostic result for an H3K27M-positive spinal lesion, although previously conducted stereotactic and open biopsies of the intracranial midline lesion were inconclusive. The morbidity associated with biopsies in certain locations may delay treatment, suggesting the need for earlier consideration of dural biopsies in patients with leptomeningeal spread. Liquid biopsy, using circulating tumor deoxyribonucleic acid in cerebrospinal fluid, is being explored as a non-invasive alternative that could potentially lead to earlier and more specific diagnoses [25]. A maximal reduction of the tumor in the posterior cranial *fossa* was conducted in our patient, which yielded a histopathological diagnosis. However, most of our patients with pontine lesions do not undergo any form of biopsy procedure. Therefore, we are eagerly waiting for the validation and implementation of liquid biopsy techniques as a diagnostic tool for these tumors. Meanwhile, based on the findings of Nazarian et al. [22] and Hoffman et al. [26], where similar mutational arrangements were observed across all disease sites, a biopsy of the metastatic sites could be considered in patients with dissemination as an alternative.

Most data on HGG dissemination patterns come from isolated case reports or small series, with no large-scale systematic studies on dissemination across specific molecular subtypes. In contrast to our case, the vast majority of midline HGGs described in the literature with dissemination and aggressive behavior in children, whether metastasizing within or outside the CNS, are associated with the H3 K27M mutation [18–22, 24, 27–35]. Some authors reported extracranial metastases of hemispheric H3.3G34R-mutant tumors in children [21, 36, 37]. There is a case of a child with leptomeningeal dissemination and poor prognosis without *H3F3A* mutation reported by Japanese authors [38]. However, the localization of this H3-wildtype and IDH-wildtype primary tumor was the frontal lobe. In contrast, Aghajan et al. [39] reported a case of a pediatric patient with an atypical anaplastic astrocytoma in the cerebellum and diffuse leptomeningeal spread that achieved long-term survival. Molecular analysis revealed unique genetic alterations, highlighting the heterogeneity of pediatric HGGs. Notably, the absence of H3 K27M and IDH mutations, *EGFR*, *p53*, *ATRX*, and *BRAF V600E*, in this case, suggests the existence of different molecular subtypes within pediatric HGGs, with a potential for a good prognosis. In our patient, H3K27me3 staining showed mostly retained nuclear expression, suggesting the absence of H3 K27M alteration. To our knowledge, this is a unique presentation of a midline HGG with leptomeningeal cranial and spinal dissemination at diagnosis without the expected molecular pattern typically associated with such cases. Unfortunately, the limited resources in Serbia, a middle-income country, pose significant constraints on our ability to conduct further investigations into tumor subtypes, perform additional IHC staining, and carry out molecular testing, which is essential for a more comprehensive characterization of this tumor.

Limited availability of diagnostic testing poses a significant challenge in accurately diagnosing CNS tumors, particularly in light of the evolving WHO 2016 and 2021 classification systems. This report highlights the difficulties encountered in low and middle-income countries (LMICs) due to the lack of modern equipment and resources for molecular analysis. These limitations significantly hinder precise diagnosis, especially for CNS tumors in children, and given that the vast majority of children live in LMICs, this represents a substantial problem. Addressing these challenges requires global collaboration and investment in accessible diagnostic technologies for LMICs, ensuring equitable access to accurate diagnosis and guiding optimal treatment for children worldwide.

The question of whether craniospinal irradiation is indicated in patients with disseminated HGGs was raised by Müller et al. [40]. The findings from their paper on craniospinal irradiation with concurrent temozolomide for primary

metastatic pediatric HGGs or DIPG indicate that this treatment approach, although feasible, is associated with limited efficacy and severe myelotoxicity. The study reported disease progression in all patients and a median OS of just over seven months. Similarly, our presented case of a 12-year-old boy with pediatric midline HGG and leptomeningeal dissemination demonstrates the challenges in managing such aggressive tumors. Our patient exhibited progression right after craniospinal radiotherapy treatment with a new lesion on the MRI of the spine at the level of Th4. Moreover, due to myelotoxicity, concomitant temozolomide was discontinued in our patient after five fractions of radiotherapy. Despite the implementation of craniospinal radiotherapy and chemotherapy, the patient experienced rapid neurological deterioration and disease progression, and eventually succumbed to the disease 13 months after the diagnosis. Benesch et al. [16] reported a median OS of 1.5 years in patients with primary disseminated HGGs treated by local radiotherapy and chemotherapy, without statistically significant differences in OS between the group with and without dissemination. So far, no form of treatment has resulted in OS benefit in disseminated HGGs, whether it was local or craniospinal radiotherapy or the addition of various chemotherapy and immunotherapy agents [15, 16, 23, 41]. These findings highlight the urgent need for more effective treatment strategies that can improve outcomes in pediatric HGGs with or without metastatic spread. Further prospective studies are warranted to develop more effective treatments for HGGs in children.

Conclusion

Pediatric high-grade gliomas, particularly diffuse midline gliomas, remain formidable entities with limited treatment options and poor prognoses. Regardless of whether they present as focal or disseminated, these tumors are associated with equally poor overall survival, and no current treatment has demonstrated a meaningful improvement in patient outcomes. Future efforts should prioritize comprehensive molecular analysis worldwide to refine our understanding of different tumor entities and guide the development of personalized treatment strategies.

Conflict of interest

The authors declare no conflict of interest.

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