Remission of Pediatric Diffuse Intrinsic Pontine Glioma: Case Report and Review of the Literature

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Background: Diffuse midline glioma (DMG) is one of the most aggressive pediatric tumors. Approximately 60% of pediatric DMG patients die within the first year of diagnosis. Complete clinical and radiological remission of DMG is extremely rare. The objective of this study was to describe a case of remission of pediatric DMG and to compare with similar cases published so far. Results: DMG was diagnosed in a 2-year-old girl who presented with brainstem and increased intracranial pressure manifestations. Ventriculoperitoneal shunt and chemotherapy-based treatment were offered. From the diagnosis, in spite of progressive enlargement of the tumoral lesion, her clinical condition improved remarkably. After the end of chemotherapy, progressive and gradual imagiological improvements occurred. At the end of the 60th month of follow-up, she was asymptomatic with total remission. Six pediatric DMG cases, from birth to the age of 3, in whom remission occurred were found in the literature. Histology sample was available in two of them (fibrillary astrocytoma—WHO Grade II and anaplastic astrocytoma—WHO Grade III). None received chemotherapy or radiotherapy. Conclusion: Remission of pediatric DMG is extremely rare and reinforces the biological heterogeneity of the tumor. In the absence of reliable predictors of prognosis, offering the best supportive treatment, including neurosurgical interventions should be considered in similar cases.

Keywords: Childhood, childhood diffuse midline glioma, remission

Background
Diffuse midline glioma (DMG) is one of the most aggressive pediatric tumors.¹ There is insufficient evidence-based data to guide the management of pediatric DMG. Approximately 60% of childhood DMG patients die within the first year of diagnosis.² The associated dismal prognosis is explained by the tumor infiltrative nature, anatomic sensitive location, transient response to radiation, and chemotherapy resistance.³

There has been no significant improvement in the treatment and prognosis of pediatric DMG in more than three decades. Discussion of atypical cases is important to improve the knowledge about the natural history of the tumor as well as to assist the discussion around prognostication.

Herein, we report a case of striking clinical and radiological regression of a pediatric DMG. An updated revision of similar published cases is presented.

Clinical Presentation
A 2-year-old girl presented with approximately 6 weeks of headache, somnolence, progressive gait impairment, and strabismus. Her examination disclosed bilateral abducens nerve palsy, mild hypotonia, truncal ataxia, gait impairment, and bilateral Babinski sign. Brain
magnetic resonance imaging (MRI) revealed a diffusely expanded pons, hyperintense in long TR sequences, without gadolinium enhancement, and hydrocephalus [Figure 1A–D]. Magnetic resonance spectroscopy (MRS) was not available. After ventriculoperitoneal shunt, she started chemotherapy with cisplatin/etoposide for 10 cycles followed by vinblastine for 52 weeks. In spite of the enlargement of the pons by 9 mm [Figure 1E–G], her clinical condition improved remarkably, with the resolution of abducens nerve palsy, ataxia, and gait impairment. Chemotherapy was stopped and the follow-up images showed a gradual decrease in signal intensity in central pons and a decrease in axial diameter by 18 mm [Figure 1H–P]. At the end of the 60th month of follow-up, she was asymptomatic and with normal developmental milestones. She remains asymptomatic for 2 years.

**Review of Other Cases**

We performed a review of similar clinical cases, published in English, between 1980 and August 2019, using the search terms vanishing, remission, regression, survival, outcome, cure, and “diffuse intrinsic pontine glioma” or “diffuse midline glioma” or “pontine glioma”. We identified five articles illustrating six patients in pediatric age [Table 1], with an equal proportion of males to females. The age of onset varied from *in utero* to 3 years old. Their ages at diagnosis varied between 2 days to 4 years. Contrast enhancement in MRI was present in two patients and three patients had hydrocephalus. A histology sample was available in one patient that revealed to be a fibrillary astrocytoma (WHO Grade II). None of them received chemotherapy or radiotherapy. All patients presented with clinical and radiological regression, occurring between 1 week to 1 year and 6 weeks to 3.5 years, respectively. They were followed up until they had 5 to 11 years of age and none presented any signs of imagological recurrence or clinical deterioration. One case of presumable DMG was excluded because of the presence of atypical findings (cystic components and intraspinal component).[9]

**Discussion**

As with other published cases of an extremely favorable outcome, our patient presented with progressive brainstem symptoms, signs of increased intracranial pressure with typical brainstem diffusing enlarging

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**Figure 1:** Brain magnetic resonance imaging (MRI) at presentation (A–D) depicting an enlarged pons with diffuse hyperintensity in long TR sequences (A), with basilar engulfment and a clear demarcation between the pons and medulla (B), without gadolinium enhancement (C). Hydrocephalus is also present (D). Follow-up axial MRI FLAIR (E-P) at the begging of chemotherapy (E), after the first (F), and second (G) week of chemotherapy, at the 2nd (H), 5th (I), 8th (J), 12th (K), 17th (L), 23rd (M), 35th (N), 48th (O), and 60th (P) months of follow-up.
| Case no. | Reference | Gender | Onset | Diagnosis | Contrast enhancement | Hydrocephalus | Histology | Treatment | Time to clinical remission onset | Time to radiological regression documentation | Last evaluation (time after diagnosis) |
|---------|-----------|--------|-------|-----------|----------------------|---------------|-----------|-----------|---------------------------------|---------------------------------------------|-----------------------------------------------|
| 1       | [4]       | F      | 3 years and 3 months | 4 years | Yes | No | NA | No | 1 year | 3 years | 5 years: nystagmus and pyramidal signs; marked radiological improvement |
| 2       | [5]       | M      | 11 months | 20 months | No | Yes | Fibrillary astrocytoma (WHO Grade II) | No | 6 weeks | 3,5 years | 6 years: normal neurological exam; normal MRI |
| 3       | [6]       | M      | In uterus | 2 days | Yes | No | NA | No | 1 week | 6 weeks | 5 years: near-normal neurological exam; marked radiological improvement |
| 4       | [6]       | F      | In uterus | 1 week | NA | No | NA | No | NA | 3 months | 10 years: near normal neurological exam; marked radiological improvement |
| 5       | [7]       | F      | 5 weeks | 11 weeks | No | Yes | NA | No | NA | 3 months | 11 years: normal neurological exam; marked radiological improvement |
| 6       | [8]       | M      | In uterus | 7 weeks | No | Yes | NA | No | 8 months | 5 months | 3.2 years: motor development corresponded to a 3-month-old; complete radiological remission |

NA = no information available

aCombination of homeopathic and natural compounds was given

bIV ventricule compression was present

cVentriculoperitoneal shunt was performed
lesion supporting the diagnosis of pediatric DMG. Initial clino-radiological dissociation with marked clinical improvement contrasting tumor enlargement occurred while on chemotherapy. For this reason, the role of chemotherapy in our patients is questionable. Nevertheless, a delayed consequence of chemotherapy or an intrinsic senescent phenotype of the tumor can occur and should be considered when trying to understand this striking favorable evolution.

An accurate DMG diagnosis is established based on MRI and clinical features in the majority of cases. Unfortunately, MRS that can aid diagnosis and longitudinal monitoring of pediatric DMG was not performed in our patient or in other similar cases found in the literature. In atypical cases, alternative brainstem tumoral and nontumoral conditions such as embryonal tumors, low-grade gliomas, inflammatory, and infectious lesions should be considered. With the long-term follow-up hindsight, the alternative diagnosis of low-grade glioma is to be considered. Of the published similar cases, biopsy was performed in just one patient and none received a specific treatment. The unavailability of biopsy precludes more valid conclusions regarding the meaning of these cases of pediatric DMG remission. Biopsy is currently indicated in atypical DMG cases as well as in the context of clinical trials when conducted by experienced neurosurgeons. Genetic heterogeneity in cases of histologically proven DMG has been demonstrated making reasonable to hypothesize that a small group of pediatric DMG patients may have a favorable outcome, whereas other, for instance, patients with K27M mutations carry a dismal prognosis. For these reasons, and because of the increase of safeness, it is questionable not to biopsy these patients. Nevertheless, these cases point that initial supportive treatment, per example hydrocephalus treatment, should always be considered.

In conclusion, our case further contributes to demonstrating that the diagnosis of DMG is not obligatorily synonymous with poor outcome and a cautious attitude when addressing these patients offering the best supportive treatment possible is reasonable.

The patient guardian has consented to the submission of the case report for submission to the journal.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Airewele G, Miller G, McCluggage C, Chintagumpala M. Lesion regression. J Neurosurg 2007;107:80-1; author reply 81.
2. Bromberg JE, Siemers MD, Taphoorn MJ. Is a “vanishing tumor” always a lymphoma? Neurology 2002;59:762-4.
3. Buhl JL, Selt F, Hiescher T, Guido R, Ecker J, Sahm F, et al. The senescence-associated secretory phenotype mediates oncogene-induced senescence in pediatric pilocytic astrocytoma. Clin Cancer Res 2019;25:1851-66.
4. Cooney T, Lane A, Bartels U, Bouffet E, Goldman S, Leary SES, et al. Contemporary survival endpoints: an international diffuse intrinsic pontine glioma registry study. Neuro Oncol 2017;19:1279-80.
5. Dellaretti M, Touzet G, Reynolds D, Dubois F, Gusmão S, Pereira JL, et al. Correlation between magnetic resonance imaging findings and histological diagnosis of intrinsic brainstem lesions in adults. Neuro Oncol 2012;14:381-5.
6. Hassan H, Pinches A, Picton S, Phillips RS. Survival rates and prognostic predictors of high grade brain stem gliomas in childhood: a systematic review and meta-analysis. J Neurooncol 2017;135:13-20.
7. Lobon-Iglesias MJ, Giraud G, Castel D, Philippe C, Debily MA, Briandet C, et al. Diffuse intrinsic pontine gliomas (DIPG) at recurrence: is there a window to test new therapies in some patients? J Neurooncol 2018;137:111-8.
8. Lenard HG, Engelbrecht V, Janssen G, Wechsler W, Tautz C. Complete remission of a diffuse pontine glioma. Neuropediatrics 1998;29:328-30.
9. Rao S, Constantini S, Gomori JM, Siegal T, Epstein F. Spontaneous involution of an intra-axial brain stem lesion: a case report. Pediatr Neurosurg 1995;23:279-81; discussion 282.
10. Schomerus L, Merkenschlager A, Kahn T, Hirsch W. Spontaneous remission of a diffuse brainstem lesion in a neonate. Pediatr Radiol 2007;37:399-402.
11. Yao Y, Li Y, Liu Y, Zhao B, Wang X. Incidence and clinicopathologic features of H3 K27M mutations in adults with radiographically-determined midline gliomas. J Neurooncol 2019;143:87-93.
12. Walker DA, Liu J, Kieran M, Jabado N, Picton S, Packer R, et al.; CPN Paris 2011 Conference Consensus Group. A multi-disciplinary consensus statement concerning surgical approaches to low-grade, high-grade astrocytomas and diffuse intrinsic pontine gliomas in childhood (CPN Paris 2011) using the Delphi method. Neuro Oncol 2013;15:462-8.
13. Warren KE, Killian K, Suuriniemi M, Wang Y, Quezado M, Meltzer PS. Genomic aberrations in pediatric diffuse intrinsic pontine gliomas. Neuro Oncol 2012;14:326-32.