Pediatric Neurosurgery

Novel Insights from Clinical Practice

Pediatr Neurosurg 2024;59:202–209
DOI: 10.1159/000542050

Received: June 7, 2024
Accepted: October 9, 2024
Published online: October 18, 2024

# Long-Term Follow-Up of a Child with EWSR1-BEND2 Fused Spinal Astroblastoma

Isabel Fernandes Arroteia[a, b] Maria Licci[a, b] Jürgen Hench[c] Andrea Bartoli[d] Marc Ansari[e, f] Pavlo Plavsky[g] Axel Terrier[a] Andre Oscar von Bueren[e] Stephan Frank[c] Jehuda Soleman[a, b, h] Raphael Guzman[a, b, h]

[a]Department of Neurosurgery, University Hospital Basel, Basel, Switzerland; [b]Department of Pediatric Neurosurgery, University Children's Hospital Basel, Basel, Switzerland; [c]Institute of Pathology, University Hospital Basel, Basel, Switzerland; [d]Department of Neurosurgery, University Hospital Geneva, Geneva, Switzerland; [e]Cansearch Research Platform for Pediatric Oncology and Hematology, Faculty of Medicine, Department of Pediatrics, Gynecology and Obstetrics, University of Geneva, Geneva, Switzerland; [f]Division of Pediatric Oncology and Hematology, Department of Women, Child and Adolescent, University Geneva Hospitals, Geneva, Switzerland; [g]Department of Pediatric Neurosurgery, OHMATDYT National Specialized Children's Hospital of MOH Ukraine, Kyiv, Ukraine; [h]Faculty of Medicine University of Basel, Basel, Switzerland

### Established Facts

- Spinal cord astroblastoma is a rare malignant tumor that primarily affects children, with a female predominance.
- Few cases of spinal cord astroblastoma have been reported in the literature so far.
- Several subtypes of astroblastoma with distinct molecular signatures have recently been described by independent study groups.
- A therapeutic strategy has not yet been established.

### Novel Insights

- This is the first published case of a pediatric spinal cord astroblastoma with long-term follow-up.
- The use of ultra-fast molecular techniques for perioperative diagnosis has the potential to influence surgical decision making and prompt the initiation of adjuvant therapy in rare central nervous system tumors.
- Surgical resection is considered the mainstay of therapy, even in the treatment of tumor recurrence, as it can improve patients' quality of life by reducing neurological deficits and pain.



karger@karger.com
www.karger.com/pne



Correspondence to:
Isabel Fernandes Arroteia, isfernan@outlook.com

**Keywords**
Pediatric neurosurgery · Neuropathology · Nanopore · Astroblastoma · Methylome · Brain tumor classifier

**Abstract**
***Introduction:*** Spinal astroblastoma is a rare highly malignant tumor that mainly affects children. We review the few cases described in the literature and highlight the challenges of managing this neoplasm by illustrating a case recently treated at our institutions. To our knowledge, this is the first published case of EWSR1-BEND2 fused spinal astroblastoma with long-term follow-up. ***Case Presentation:*** An 8-year-old girl was transferred from her home country to Switzerland for treatment of a recurrent intramedullary tumor of the cervical spine extending from C2-C7. The tumor was primarily diagnosed as an ependymoma of the spinal cord. Prior to her transfer to our department, the patient had undergone subtotal resection of the lesion, radiation therapy, multiple chemotherapy regimens, and biopsy of the recurrent tumor. Clinically, the patient presented with tetraparesis and had recently experienced worsening upper extremity weakness with complete loss of hand function. We performed a near total resection of the recurrent tumor. Ultra-fast Nanopore seq® based DNA methylome profiling allowed confirmation of the molecular diagnosis of a high-grade neuroepithelial tumor (HGNET-MN1) consistent with astroblastoma in less than 2 h, with subsequent molecular workup revealing a EWSR1-BEND2 fusion. After surgery, the patient gradually regained function in her hands. She was sent to a specialized pediatric rehabilitation center, and while the tumor was being followed radiologically with no adjuvant treatment planned, the patient presented with a relapse of the tumor in only 3 months. Given the acute worsening of radiating pain and sudden respiratory failure, a cervical decompression was performed. MRI of the cervical spine showed infiltration of the lower aspects of the brainstem. The patient was offered palliative comfort care. ***Conclusion:*** Spinal astroblastoma is a rare and highly aggressive tumor affecting children and young adults with a high recurrence rate and thus far not well-defined prognosis. The molecular signature of astroblastoma needs to be further characterized to establish a treatment-relevant classification and to allow a better prognostication. Currently, gross-total resection combined with radiotherapy remains the mainstay of treatment for spinal astroblastoma.



## Introduction

Astroblastoma is a rare high-grade neuroepithelial tumor usually occurring in children and young adults with a clear female predominance, typically located in the cerebral hemispheres [1–7]. Very few cases of spinal astroblastoma have been described in the literature so far. Astroblastoma was first described as a distinct tumor entity by Bailey and Cushing in 1926 [8–11]. These tumors have diverse morphological features with overlapping astrocytic and ependymal characteristics. The typical histopathological appearance is the astroblastomatous rosette, which is also seen in other central nervous system (CNS) tumors [12], including BRAF-mutant pleomorphic xanthoastrocytoma, ZFTA-fused supratentorial ependymoma, and IDH wild-type glioblastoma [13]. Recent advances in molecular diagnostics have allowed further differentiation of astroblastoma from other tumors. Seventy percent of tumors histologically classified as astroblastoma have a structural rearrangement in the MN1 proto-oncogene on chromosome 22. MN1-altered astroblastomas were described in 2016 by Sturm et al. [14] as a distinct epigenetic tumor cluster, characterized as high-grade neuroepithelial tumors of the CNS with MN1-alteration (HGNET-MN1). Although the identification of an MN1-alteration classifies astroblastoma as a type of circumscribed astrocytic glioma in the WHO 2021 CNS Tumor Classification, it is not required for diagnosis. MN1-altered astroblastoma probably represents a variant of astroblastoma.

Investigation of the molecular signature of these tumors is critical for the development of targeted therapies. EWSR1-BEND2 fusion was first described by Tsutsui et al. in 2021. Since then, several cases of spinal astroblastoma with the same fusion have been published. The *EWSR1* gene is ubiquitously expressed in most cell types and plays an epigenetic role in gene expression, RNA processing, and cellular signaling [15]. In several malignancies, the N-terminal activation domain of EWSR1 has been shown to fuse with the DNA-binding domain of several transcription factors, leading to the generation of oncogenic transcription factors [16]. The direct role of the EWSR1-BEND2 fusion in tumorigenesis remains to be determined [17]. EWSR1 fusion appears to be more common in brainstem and spinal cord astroblastomas compared to MN1 fusion in hemispheric astroblastomas, which previously led to the speculation that these represent two distinct subtypes of astroblastoma [13]. Due to the rarity of this tumor, a differentiated therapeutic strategy has not yet been established.

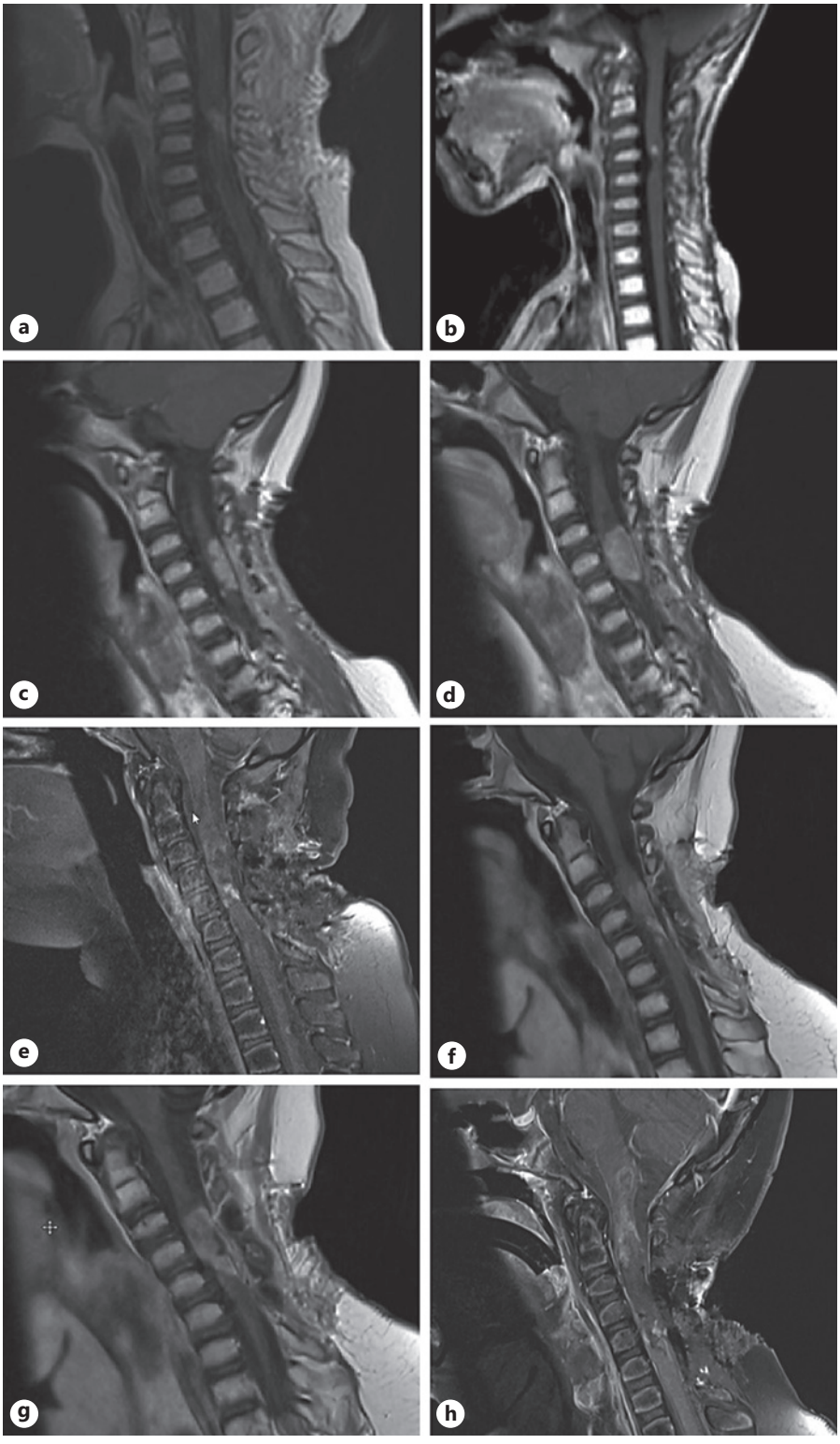


**Fig. 1. a–h** Successive contrast-enhanced cervical MRIs showing the evolution of tumor mass over time. **a** Cervical MRI at the time after subtotal resection (03/2017). **b** MRI showing tumor progression after subtotal resection and radiation therapy (03/2018). **c** MRI showing increase in tumor size 63 months after primary surgery. **d** Progression of the tumor compared to the MRI performed 2 months earlier, in the context of a gradual deterioration of distal strength in the upper extremities and respiratory failure (09/2023). **e** Postoperative MRI showing a gross-total resection of the tumor (10/2023). **f** A tumor recurrence was diagnosed only 3 months after near total resection at our institution. **g** Three months later, the FU MRI showed tumor progression. **h** MRI showing a significant enlargement of the tumor with infiltration of the brainstem.

## Case Presentation

A 3-year-old girl was diagnosed with a C2-C7 intramedullary tumor in the clinical context of limping in her right leg. Partial resection of the tumor was performed (Fig. 1a), resulting in complete postoperative paraplegia and weakness of both upper extremities. The histopathologic diagnosis was compatible with an anaplastic ependymoma. Subsequently, the patient underwent two cycles of chemotherapy (HIT-SKK chemotherapy) [18, 19] followed by spinal radiotherapy with a total dose of 44.2 Gy. Twelve months after surgery, follow-up (FU) MRI revealed tumor progression (Fig. 1b). A chemotherapy regimen of 6 cycles of Vincristine-Irinotecan-Temodal was discontinued after four cycles due to severe intolerance. Subsequent MRI scans showed no further tumor progression.

Sixty-three months after the primary surgery, at the age of 8, an MRI showed new progression of the disease (Fig. 1c). At this point, the family moved from their home country to Switzerland, where they were referred to another institution within the country. At this stage, the patient had severe tetraparesis with partial distal movement in the upper limbs and limited bladder control (mostly diurnal). After discussion with the family and in order to preserve her functions as well as to confirm diagnosis, an open biopsy was performed 3 months after the radiological diagnosis of recurrence. The patient's neurological status remained unchanged after surgery. An Individualized Molecular Tumor Analysis (INFORM) revealed an EWSR1-BEND2 fusion, consistent with the diagnosis of astroblastoma. Two months later, a new progression of the tumor was observed on MRI. An ambulatory treatment strategy appeared in this heavily pretreated patient most appropriate, thus a treatment according to MEMMAT protocol [20] was initiated. A ventricular drain with Omaya reservoir and a port-a-cath were implanted. Over the course of treatment, the patient remained stable over many months before showing progressive impairment of hand dexterity, limited bilateral hand movements, and the known spastic paraparesis. Eleven months after resuming chemotherapy, she presented with rapidly progressive upper extremity weakness and diurnal urinary incontinence, as well as severe pain requiring the use of opioid medication. She was admitted to the hospital for respiratory distress, at which time MRI revealed tumor progression and the development of perifocal edema (Fig. 1d). Antiepileptic treatment had to be initiated due to the onset of seizures despite the absence of abnormalities on cranial MRI. The patient was transferred to our institution for further surgical management. On arrival, she presented with impaired hand dexterity, limited bilateral hand movements, and spastic tetraparesis. After thorough discussion, we recommended surgical resection of the tumor recurrence due to clinical and radiologic progression, which occurred 17 months after the second recurrence and 13 months after initiation of palliative chemotherapy, respectively. We performed a re-laminoplasty (C2-C7) and a near total resection was achieved. Intraoperative ultrasound was used to determinate the tumor extent and guide resection. Surgery was performed under continuous neuromonitoring with standard measurements (D-wave as well as motor evoked potentials, direct nerve, and spinal cord stimulation). Electrophysiologic recordings remained unchanged throughout the surgery. Skin closure was performed with the Dermabond® Prineo® Skin Closure System [21]. Postoperative imaging confirmed near total resection of the tumor (Fig. 1e). A few days after surgery, the patient developed a cerebrospinal fluid fistula requiring operative wound revision and lumbar drain implantation. The wound remained dry thereafter. Perioperative ultra-rapid methylome analysis with nanopore sequencing [22, 23] revealed a high-grade neuroepithelial tumor (HGNET-MN1) consistent with astroblastoma. RNA sequencing of the tumor tissue showed evidence of an EWSR1 (exon 7)-BEND2 (exon 2) fusion. Histopathologic analysis revealed a Ki-67 proliferation index of 30–40%. The patient's postoperative recovery was characterized by early mobilization to a wheelchair and progressive improvement of motor function in both hands and significant pain reduction. One week after revision surgery, the patient was able to resume one of her favorite activities – using a tablet. Early transfer to a pediatric rehabilitation center was arranged.

Since no molecular target was identified, and the disease thus far showed only relatively slow regrowth, there were no recommendations for immediate adjuvant therapy following the tumor board discussion involving neuro-oncologists from both centers involved in the patient management. Accordingly, the decision was made to follow up the tumor with radiologic imaging and clinical FU without any further adjuvant treatment and to perform an intensive rehabilitation program. Three months later, the FU MRI showed tumor progression (Fig. 1f). The patient experienced rapid clinical deterioration; she developed acute radiating pain and respiratory insufficiency while being treated by high-dose morphine for pain management. A decision was made to perform a cervical cord decompression, which provided significant pain relief. Ablation of the breathing tube was not possible

**Table 1.** Summary of published case reports on spinal astroblastoma and current case

| Publication | *N* | Age at diagnosis | Tumor range | Extent of resection | Adjuvant therapy | Survival/FU time | Molecular alteration |
|---|---|---|---|---|---|---|---|
| Yamasaki et al. [24] (2020) | 1 | 3 months | Medulla-C4 | STR | TMZ, ETP, bevacizumab | 1-month survival | EWSR1-BEND2 |
| Mugge et al. [25] (2023) | 1 | 11 months | C0-T4 | GTR | None | Not reported | MN1-alteration, changes in *APC* and *LRP1B* gene |
| Lucas et al. [13] (2022) | 1 | 6 years | C3-C7 | Biopsy | None | Recurrence at 12 months 25-month survival | EWSR1-BEND2 |
| Rao et al. [26] (2022) | 1 | 16 years | T11-T12 | GTR | TMZ, IMRT | No recurrence at 6 months of FU | MN1-alteration |
| Current case | 1 | 3 years | C2-C7 | GTR | HIT-SKK protocol, radiotherapy, 6 cycles of vincristine-irinotecan-TMZ, modified-MEMMAT protocol [5] | 87 months of FU | EWSR1-BEND2 |

FU, follow-up; STR, subtotal resection; GTR, gross-total resection; TMZ, temozolomide; ETP, etoposide; IMRT, intensity-modulated radiation therapy.

due to insufficient breathing capacity. The following MRI showed a significant enlargement of the tumor with infiltration of the brainstem (Fig. 1g). The patient was offered palliative comfort care. One month after decompressive surgery, she showed complete tetraplegia, dependence on mechanical ventilation, and the ability to communicate through sounds, facial expressions, and eye movements. This raised significant ethical questions about how to proceed. A watchful waiting approach was adopted in conjunction with comfort care. The patient passed away 87 months after initial surgery.

## Discussion

We present a case of spinal astroblastoma in a 3-year-old child. To our knowledge, only 4 cases of spinal astroblastoma in children have been reported in the literature (Table 1). Because the tumor was initially – without molecular analyses – considered as ependymoma, our patient was treated according to the German strategy with HIT-SKK chemotherapy, local irradiation, and four cycles of vincristine-irinotecan-temozolomide after the first recurrence. With the increased accessibility of molecular diagnostic tools and the inclusion of molecular markers in the WHO classification of 2021, the diagnosis was refined to astroblastoma during the re-examination of initial tumor samples in Switzerland in 2022.

MN1-altered astroblastoma occurs mainly in children under the age of fifteen and has a marked female predominance [27]. They typically arise in the cerebral hemispheres and often present with seizures [27]. Spinal astroblastomas present with typical symptoms of intramedullary lesions, depending on the location, size, and growth rate of the tumor. Common symptoms include neck and back pain, sensory changes, motor weakness, bowel and bladder dysfunction, incoordination, spasticity, and pain.

Regardless of tumor location, the prognosis of MN1-altered astroblastoma is known to be poor. The 5- and 10-year progression-free survival rates for cerebral astroblastoma are 38% and 0%, respectively, while the 5- and 10-year overall survival rates are 89% and 55%, respectively [27]. No prognostic data are available for spinal cord astroblastoma due to the rarity of this entity. The progression-free survival of the few published pediatric cases is variable, even in children who have benefited from gross-total resection and adjuvant chemo- and radiotherapy. Of the four previously described cases of spinal astroblastoma in pediatric patients (Table 1), 1 case showed no recurrence at 6 months after gross-total resection (GTR) [26] followed by adjuvant temozolomide

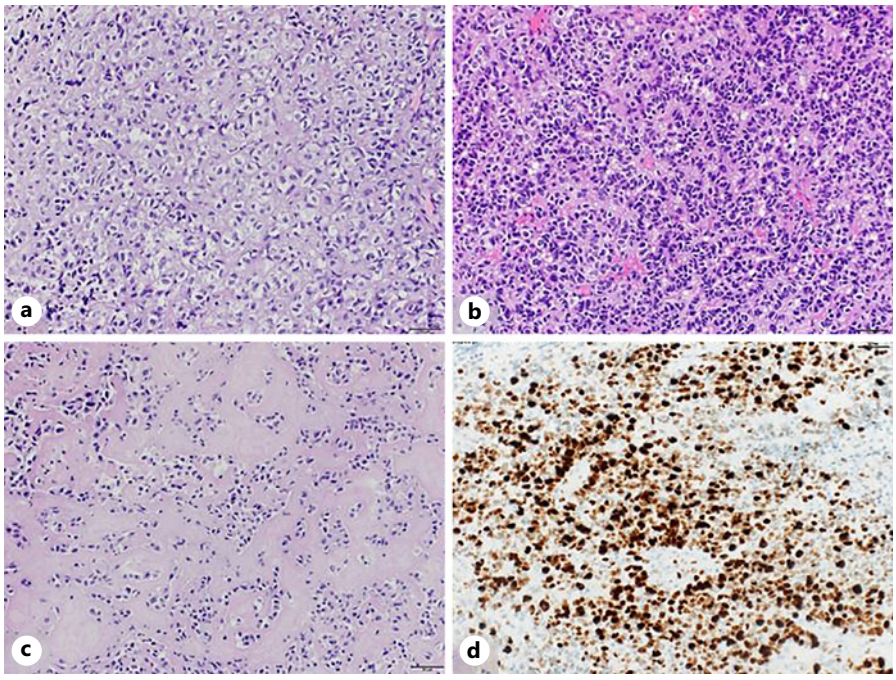


**Fig. 2. a–c** Illustration of the variability in histologic appearance of the same tumor, highlighting the importance of accurate molecular diagnostics. **a** Microscopic imaging shows a histologically malignant, highly cellular tumor. **b** Histological imaging of tumor tissue showing a clear cell appearance. **c** Histological image exhibiting a marked tendency to sclerosis. **d** Ki-67 staining of the tumor showing a high proliferation index.

and intensity-modulated radiotherapy. In 2 cases where GTR could not be achieved, patients died at 1-month and 25-month FU, respectively [13, 24]. The latter patient showed tumor progression at 12 months after tumor biopsy and no adjuvant therapy was administered. In 1 case, no precise FU data were published [25]. Our case is the first describing long-term FU.

Despite the potential contribution of chemotherapeutic treatment in achieving long-term survival in our patient, eventual tumor progression resulted in an increase of motor disability, leading to a decline in the patient's quality of life. This ultimately necessitated surgical resection to treat the neurological deficits. Surgery, established as the primary treatment for hemispheric astroblastoma, appears to have potential benefits and merits repetitive consideration in cases of spinal astroblastoma. Specialized care, particularly in dedicated centers with competent surgical and pathologic capabilities, is critical.

Microscopic examination of astroblastoma typically shows perivascularly arranged tumor cells with thick cell processes extending to a central hyalinized vessel, termed astroblastic pseudorosettes, which are also seen in other CNS tumors. According to cIMPACT-NOW recommendations, identification of MN1 fusion by next-generation sequencing or MN1 rearrangement by break-apart fluorescence in situ hybridization may be used to aid in the diagnosis of MN1-altered astroblastoma [28]. No formal tumor grade is assigned to astroblastoma in the 5th edition of the WHO CNS tumor classification [29]. Molecular diagnosis can be performed using ultra-fast tumor DNA methylation profiling based on nanopore sequencing [22, 23, 30]. Epigenetic analysis of tumor tissue is becoming increasingly important in personalized oncology and has recently been defined by the WHO as a standard of care in the classification of CNS tumors [31]. Genome-wide copy number profiles obtained in parallel with DNA methylation further contribute to molecular tumor diagnostics [32, 33]. Artificial intelligence-based methylome analysis and copy number profiling can rightly be considered the most advanced and clinically implemented branch of digital pathology [34]. While most routine diagnostic methylation profiling is performed on microarrays, only a few institutions are using same-day nanopore sequencing as an ultra-rapid alternative for both DNA methylation and copy number alteration detection. Nanopore sequencing has become one of the most powerful sequencing technologies since its development, enabling whole genome sequencing and disease diagnosis with high speed and cost-effective performance. Our institution uses nanopore sequencing coupled with ultra-fast supervised and unsupervised machine learning algorithms for complete methylome analysis and tumor classification within a few hours after tissue sampling [22]. This technology is of great interest in brain tumor surgery, where knowledge of the exact

molecular diagnosis may have a direct impact on surgical strategy. Perioperative frozen section analysis by pathologists, which has been used to approximate the diagnosis, is prone to diagnostic error and lack of precision. Figure 2 shows the heterogeneity of the histopathologic presentation of astroblastoma, highlighting the importance of molecular diagnostics. The implementation of point-of-care tumor methylome analysis using nanopore sequencing, coupled with a locally developed epigenomic tumor diagnostic resource platform (EpiDiP/NanoDiP) [22], has the potential to revolutionize in-surgical decision making and also allow for a rapid transition to adjuvant therapy if needed. EpiDiP/NanoDiP is a comprehensive DNA methylation and copy number profiling suite designed as an open source, image-free digital pathology tool. This technology enables WHO-compliant methylome and copy number analysis even in low- and middle-income regions that may not have access to expensive technologies such as immunohistochemistry, conventional sequencing or array-based approaches to methylome profiling.

Due to the rarity of MN1-altered spinal astroblastoma, there are no detailed guidelines for the treatment of these tumors. We consider GTR to be the main treatment modality, allowing for improvement of neurological symptoms and reduction of tumor burden, thus improving the potential response to adjuvant therapies. Since astroblastoma is considered a glial tumor with a tendency to an aggressive course, some groups advocate the use of an adjuvant chemotherapy regimen with temozolomide, concomitant and subsequent to radiotherapy in cerebral astroblastoma [12]. Radiation doses up to 45 Gray can be safely used to treat spinal cord tumors in children. However, early recurrence has been described in the literature, and the treatment of these tumors remains challenging. Throughout the course of the disease, our patient underwent subtotal resection, biopsy, and near total resection of tumor recurrence, along with three different chemotherapy regimens and radiotherapy. These interventions contributed to long-term survival with improved quality of life.

In conclusion, spinal astroblastoma can present with different molecular signatures. To the best of our knowledge, this is the first published case of EWSR1-BEND2 fused spinal astroblastoma with long-term FU. EWSR1-BEND2 fused spinal astroblastoma is a rare tumor affecting children and adolescents. The few cases described in the literature showed recurrence after resection, adjuvant chemotherapy and radiotherapy. To enable potential targeted therapy in the future, further research into molecular targets is warranted.

## Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from a parent of the study participant to participate in the study. Written informed consent was obtained from a parent of the participant for the publication of the details of their medical case and any accompanying images.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


## Funding Sources

I.F.A. is enrolled in a fellowship in pediatric neurosurgery partially funded by a grant received by the André et Michel Bouriez Foundation. The funder had no role in the design, data collection, data analysis, and reporting of this study.


## Author Contributions

I.F.A.: first author. M.L., J.H., A.B., M.A., P.P., A.T., A.v.B., S.F., J.S.: contribution to the conception of the work, article review and approval of final version. R.G.: principal investigator, contribution to the conception of the work, article review, and approval of final version.

## Data Availability Statement

Due to the nature of the research, supporting data are not available. Further inquiries can be directed to the corresponding author.

## References


1 Hammas N, Senhaji N, Alaoui Lamrani MY, Bennis S, Chaoui EM, El Fatemi H, et al. Astroblastoma: a rare and challenging tumor–a case report and review of the literature. J Med Case Rep. 2018;12(1):102. https://doi.org/10.1186/s13256-018-1623-1

2 Agarwal V, Mally R, Palande DA, Velho V. Cerebral astroblastoma: a case report and review of literature. Asian J Neurosurg. 2012;7(2):98–100. https://doi.org/10.4103/1793-5482.98657

3 Shen F, Chen L-C, Yao Y, Zhou L-F. Astroblastoma: rare incidence and challenges in the pattern of care. World Neurosurg. 2014;82(1–2):e125–127. https://doi.org/10.1016/j.wneu.2014.03.008

4 Port JD, Brat DJ, Burger PC, Pomper MG. Astroblastoma: radiologic-pathologic correlation and distinction from ependymoma. AJNR Am J Neuroradiol. 2002;23(2):243–7.

5 Singh DK, Singh N, Singh R, Husain N. Cerebral astroblastoma: a radiopathological diagnosis. J Pediatr Neurosci. 2014;9(1):45–7. https://doi.org/10.4103/1817-1745.131485

6 Ahmed KA, Allen PK, Mahajan A, Brown PD, Ghia AJ. Astroblastomas: a surveillance, epidemiology, and end results (SEER)-based patterns of care analysis. World Neurosurg. 2014;82(1–2):e291–297. https://doi.org/10.1016/j.wneu.2013.10.035
7 Notarianni C, Akin M, Fowler M, Nanda A. Brainstem astroblastoma: a case report and review of the literature. Surg Neurol. 2008;69(2):201–5. https://doi.org/10.1016/j.surneu.2006.12.045
8 Bailey P. Cellular types in primary tumors of the brain. In: Cellular types in primary tumors of the brain. Hoeber. New York: Reprinted by Hafner; 1932.
9 Bailev P, Bucy P. Astroblastomas of the brain. Acta Psychiatr Scand. 1930;5(3):439–61. https://doi.org/10.1111/j.1600-0447.1930.tb08230.x
10 Bailey P, Cushing H. A classification of the tumors of the glioma group on a histogenic basis with a correlation study of prognosis. Philadelphia: Lippincott; 1926.
11 Yamada SM, Tomita Y, Shibui S, Takahashi M, Kawamoto M, Nobusawa S, et al. Primary spinal cord astroblastoma: case report. J Neurosurg Spine. 2018;28(6):642–6. https://doi.org/10.3171/2017.9.SPINE161302
12 Salvati M, D'Elia A, Brogna C, Frati A, Antonelli M, Giangaspero F, et al. Cerebral astroblastoma: analysis of six cases and critical review of treatment options. J Neuro Oncol. 2009;93(3):369–78. https://doi.org/10.1007/s11060-008-9789-9
13 Lucas C-HG, Gupta R, Wu J, Shah K, Ravindranathan A, Barreto J, et al. EWSR1-BEND2 fusion defines an epigenetically distinct subtype of astroblastoma. Acta Neuropathol Berl. 2022;143(1):109–13. https://doi.org/10.1007/s00401-021-02388-y
14 Sturm D, Orr BA, Toprak UH, Hovestadt V, Jones DTW, Capper D, et al. New brain tumor entities emerge from molecular classification of CNS-PNETs. Cell. 2016;164(5):1060–72. https://doi.org/10.1016/j.cell.2016.01.015
15 Lee J, Nguyen PT, Shim HS, Hyeon SJ, Im H, Choi M-H, et al. EWSR1, a multifunctional protein, regulates cellular function and aging via genetic and epigenetic pathways. Biochim Biophys Acta Mol Basis Dis. 2019;1865(7):1938–45. https://doi.org/10.1016/j.bbadis.2018.10.042
16 Kim J, Pelletier J. Molecular genetics of chromosome translocations involving EWS and related family members. Physiol Genomics. 1999;1(3):127–38. https://doi.org/10.1152/physiolgenomics.1999.1.3.127
17 Tsutsui T, Arakawa Y, Makino Y, Kataoka H, Mineharu Y, Naito K, et al. Spinal cord astroblastoma with EWSR1-BEND2 fusion classified as HGNET-MN1 by methylation classification: a case report. Brain Tumor Pathol. 2021;38(4):283–9. https://doi.org/10.1007/s10014-021-00412-3
18 Rutkowski S, Bode U, Deinlein F, Ottensmeier H, Warmuth-Metz M, Soerensen N, et al. Treatment of early childhood medulloblastoma by postoperative chemotherapy alone. N Engl J Med. 2005;352(10):978–86. https://doi.org/10.1056/NEJMoa042176
19 von Bueren AO, von Hoff K, Pietsch T, Gerber NU, Warmuth-Metz M, Deinlein F, et al. Treatment of young children with localized medulloblastoma by chemotherapy alone: results of the prospective, multicenter trial HIT 2000 confirming the prognostic impact of histology. Neuro Oncol. 2011;13(6):669–79. https://doi.org/10.1093/neuonc/nor025
20 Peyrl A. A phase II study of metronomic and targeted anti-angiogenesis therapy for children with recurrent/progressive medulloblastoma, ependymoma and ATRT. clinicaltrials.gov. 2023. [cited 2024 Jan 1].Available from: https://clinicaltrials.gov/study/NCT01356290
21 Stricker S, Eberhard N, Licci M, Greuter L, Zweifel C, Guzman R, et al. Wound closure with a mesh and liquid tissue adhesive (Dermabond Prineo) system in pediatric spine surgery: a prospective single-center cohort study incorporating parent-reported outcome measures. J Neurosurg Pediatr. 2022;30(6):624–32. https://doi.org/10.3171/2022.8.PEDS22270
22 Hench J, Hultschig C, Brugger J, Mariani L, Guzman R, Soleman J, et al. EpiDiP/NanoDiP: a versatile unsupervised machine learning edge computing platform for epigenomic tumour diagnostics. Acta Neuropathol Commun. 2024;12(1):51. https://doi.org/10.1186/s40478-024-01759-2
23 Kuschel LP, Hench J, Frank S, Hench IB, Girard E, Blanluet M, et al. Robust methylation-based classification of brain tumours using nanopore sequencing. Neuropathol Appl Neurobiol. 2023;49(1):e12856. https://doi.org/10.1111/nan.12856
24 Yamasaki K, Nakano Y, Nobusawa S, Okuhiro Y, Fukushima H, Inoue T, et al. Spinal cord astroblastoma with an *EWSR1-BEND2* fusion classified as a high-grade neuroepithelial tumour with *MN1* alteration. Neuropathol Appl Neurobiol. 2020;46(2):190–3. https://doi.org/10.1111/nan.12593
25 Mugge L, Dang DD, Stabingas K, Keating G, Rossi C, Keating R. MN1 altered astroblastoma with APC and LRP1B gene mutations: a unique variant in the cervical spine of a pediatric patient. Childs Nerv Syst. 2023;39(5):1309–15. https://doi.org/10.1007/s00381-022-05795-y
26 Rao S, Nufina TA, Sugur H, Arumalla K, Devi BI, Santosh V. Spinal astroblastoma: a rare tumour in an unusual location. Childs Nerv Syst. 2022;38(9):1797–801. https://doi.org/10.1007/s00381-022-05468-w
27 Chen W, Soon YY, Pratiseyo PD, Sutanto R, Hendriansyah L, Kuick CH, et al. Central nervous system neuroepithelial tumors with MN1-alteration: an individual patient data meta-analysis of 73 cases. Brain Tumor Pathol. 2020;37(4):145–53. https://doi.org/10.1007/s10014-020-00372-0
28 cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. PubMed [Internet]. [cited 2023 Nov 22]. Available from: https://pubmed.ncbi.nlm.nih.gov/32307792/
29 Osborn AG, Louis DN, Poussaint TY, Linscott LL, Salzman KL. The 2021 world health organization classification of tumors of the central nervous system: what neuroradiologists need to know. AJNR Am J Neuroradiol. 2022;43(7):928–37. https://doi.org/10.3174/ajnr.A7462
30 Vermeulen C, Pagès-Gallego M, Kester L, Kranendonk MEG, Wesseling P, Verburg N, et al. Ultra-fast deep-learned CNS tumour classification during surgery. Nature. 2023;622(7984):842–9. https://doi.org/10.1038/s41586-023-06615-2
31 Komori T. [The 2021 WHO classification of tumors, 5th edition, central nervous system tumors: a short review]. Brain Nerve Shinkei Kenkyu No Shinpo. 2022;74(6):803–9. https://doi.org/10.11477/mf.1416202124
32 Euskirchen P, Bielle F, Labreche K, Kloosterman WP, Rosenberg S, Daniau M, et al. Same-day genomic and epigenomic diagnosis of brain tumors using real-time nanopore sequencing. Acta Neuropathol Berl. 2017;134(5):691–703. https://doi.org/10.1007/s00401-017-1743-5
33 Capper D, Jones DTW, Sill M, Hovestadt V, Schrimpf D, Sturm D, et al. DNA methylation-based classification of central nervous system tumours. Nature. 2018;555(7697):469–74. https://doi.org/10.1038/nature26000
34 Karimi S, Zuccato JA, Mamatjan Y, Mansouri S, Suppiah S, Nassiri F, et al. The central nervous system tumor methylation classifier changes neuro-oncology practice for challenging brain tumor diagnoses and directly impacts patient care. Clin Epigenetics. 2019;11(1):185. https://doi.org/10.1186/s13148-019-0766-2