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Anaplastic Ganglioglioma: A Very Rare Intramedullary Spinal Cord Tumor

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Key Words

Anaplastic ganglioglioma · Spinal cord · Children · Primary intramedullary spinal cord tumor · Adjuvant radiochemotherapy · Gross total resection · Temozolomide · Progression-free survival

Abstract

Gangliogliomas (GGs) are a small subset of intramedullary spinal cord tumors in children. The anaplastic variant (WHO grade III) appears to be an extreme rarity. A literature research revealed only 15 case reports of intramedullary anaplastic GGs (aGGs) and only 4 pediatric patients. The course of an 18-month-old boy with sudden onset of paraparesis is presented. Spinal MRI revealed a contrast-enhancing intramedullary tumor ranging from T6 to T12. The patient underwent a standard laminectomy/laminoplasty and gross total resection of the lesion. His neurological status remained unchanged postoperatively and he recovered very well during outpatient neurorehabilitation. Neuropathologic examination revealed an aGG of WHO grade III. Because of the high-grade histology, adjuvant radiotherapy and chemotherapy with temozolomide were administered. The patient subsequently recovered to a normal functional status. Clinical and radiographic progression-free survival is now 4 years. Based

on an extensive literature review, this is only the fifth pediatric patient with a primary intramedullary aGG and the second with documented progression-free survival of over 4 years. Another 4 primary intramedullary aGGs in adults and 7 patients with spinal dissemination from a cerebral aGG or malignant transformation of a low-grade GG have been reported. In comparison to the published case reports, which often indicate significant neurological dysfunction and rather short survival, the neurological recovery in this patient was favorable, and the oncologic outcome even more so. This is an argument for the use of the aggressive treatment regimen of complete resection followed by radio- and chemotherapy applied here.

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Introduction

Gangliogliomas (GGs) are a rather rare entity among the primary central nervous system neoplasms and account for 1% of all central nervous system tumors and approximately 4% of pediatric central nervous system tumors [1]. They show a biphasic morphologic pattern of either a predominant neuronal phenotype or else prominent glial elements [2]. The anaplastic variant (WHO

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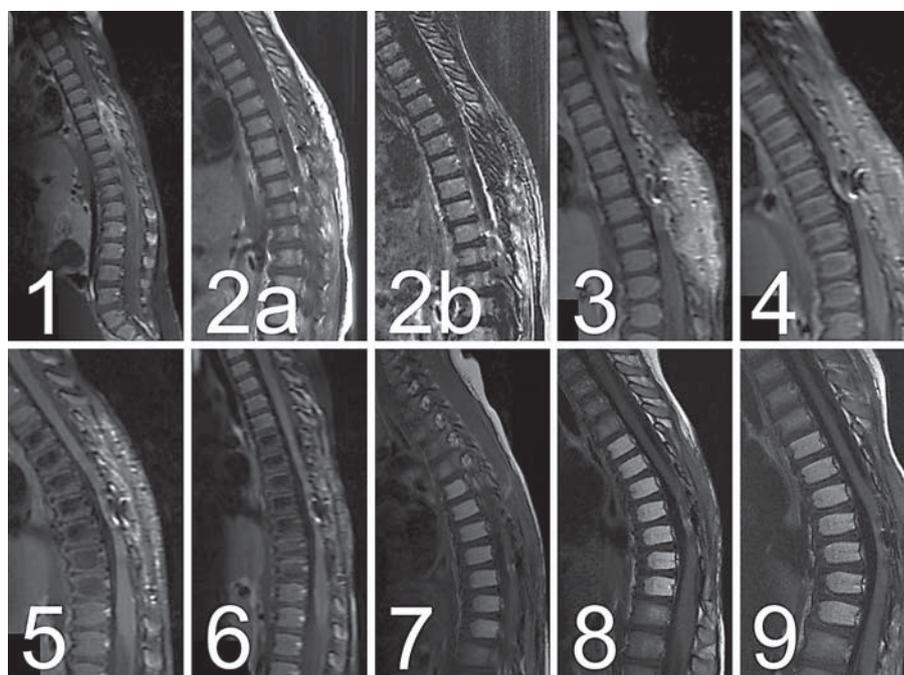
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Fig. 1. Serial MRI of the patient's thoracic spine. Panel 1: preoperative situation (T1 with contrast); panel 2: postoperative situation (2a: T1 with contrast; 2b: subtraction imaging, T1 with contrast minus T1 native); panel 3: situation at 1 month (T1 with contrast); panel 4: situation at 4 months, after completion of radiotherapy (T1 with contrast); panel 5: situation at 9 months (T1 with contrast); panel 6: situation at 1 year (T1 with contrast); panel 7: situation at 2 years (T1 with contrast); panel 8: situation at 3 years (T1 with contrast); panel 9: situation at 4 years (T1 with contrast).



grade III) is encountered only very rarely – about 5% of all GGs are anaplastic – and predominantly affects patients in their late twenties [3]. Anaplastic GGs (aGGs) have areas of pronounced hypercellularity, vascular proliferations, necrosis and many mitotic figures, especially in their glial component [4]. Only 15 case reports exist of aGGs occurring in the spinal cord, 5 of them as a result of spinal dissemination of a cerebral aGG (metastatic spinal aGG) and 2 with histological and cytogenetic evidence of malignant transformation of a former low-grade GG (secondary spinal aGG). Of the remaining 8 primary spinal cord aGGs, only 4 were reported in pediatric patients [1, 3–12].

We present the course of an 18-month-old boy who was diagnosed with a primary intramedullary aGG ranging from T6 to T12. The treatment approach is delineated and discussed.

Case Report

Clinical Features and Surgery

A boy of 18 months with normal prior development was evaluated with a recent history of repeated episodes of frequent falls and walking difficulties. Clinical examination revealed a significant paraparesis. MRI of the spine showed a contrast-enhancing mass lesion ranging from T6 to T12 (fig. 1, panel 1). Initially, a typical low-grade tumor was suspected and complete surgical re-

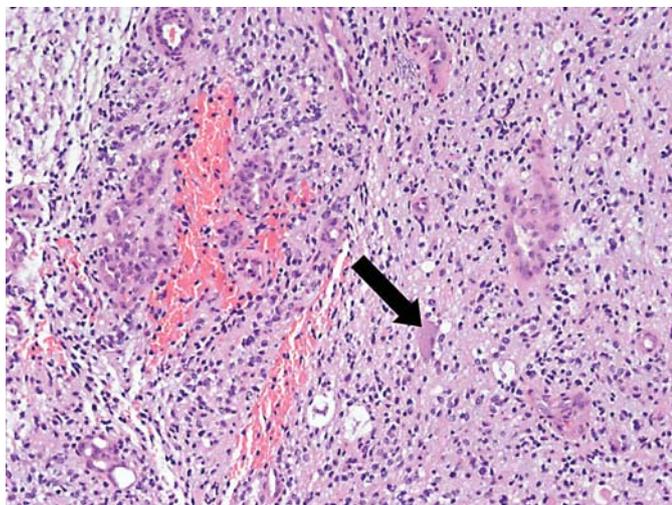
section was recommended. Prior to surgery, the patient could not walk and could stand only briefly with a caregiver's support. Babinski's sign was positive bilaterally. A standard laminotomy/laminoplasty from T6 to T12 was performed and a gross total resection of the tumor achieved, with intraoperative neurophysiologic documentation of functionally intact motor pathways. Postoperative neurologic status remained unchanged, and postoperative recovery was uneventful. During outpatient neurorehabilitation, the patient recovered very well and has achieved a normal functional status and a practically normal subsequent motor development allowing all activities, including sports (i.e. skiing).

Neuroimaging Findings

Figure 1 shows serial MRIs from before surgery to the most recent scan 4 years after diagnosis. Early postoperative imaging demonstrated the gross total resection (fig. 1, panel 2b). Follow-up imaging of the thoracic spine shows no evidence of tumor recurrence and no significant spinal deformity.

Histological Features

Histological examination revealed a moderately cellular glioneuronal neoplasm with glomeruloid proliferation of small-caliber blood vessels and focal zones of necrosis. The tumor was predominantly composed of atypical glial cells with moderate nuclear pleomorphism. Several mitotic figures could be demonstrated. An apparent biphasic growth pattern was not present, but some loosely distributed so-called dysplastic ganglion cells were observed (fig. 2, arrow). Structures typical for a long-standing or slow-growing process (Rosenthal fibers or eosinophilic granular bodies) were not encountered.



Color version available online

Fig. 2. Standard hematoxylin-eosin stain of the resection specimen (×200). Arrow: dysplastic ganglion cell. Left half of the image: glomeruloid vascular proliferation.

Immunohistochemical examination confirmed the glial nature of the tumor (positive glial fibrillary acidic protein stain of the spindle-shaped and ganglioid cellular elements). Staining for synaptophysin and CD34 identified the neuronal component. In addition, CD34 identified some so-called satellite cells. The Ki-67 proliferative index was approximately 10%.

Taken together, the following features warranted the diagnosis of an aGG (WHO grade III): mitotic activity and vascular proliferation in the context of focal necrosis in a glioneuronal tumor with nuclear atypia.

Conclusive histological diagnosis was provided by the Institute for Neuropathology at the University Hospital of Zurich and reconfirmed by the Brain Tumor Reference Center in Bonn.

Treatment Protocol and Outcome

In the face of a highly unusual histological diagnosis, adjuvant treatment was discussed extensively. After an aggressive and successful resection, an aggressive curative treatment plan with radiotherapy and temozolomide chemotherapy was devised. The patient received percutaneous radiotherapy from T4 to T10 in 26 fractions of 1.8 Gy, resulting in a treatment dose of 46.8 Gy and an additional cumulative diagnostic radiation dose of 4 Gy, adding up to a total radiation dose of 50.8 Gy to the spine. Concomitant administration of temozolomide (75 mg/m²/day) had to be interrupted after 17 days because of leukopenia, but was reinstalled 6 weeks later at a dose of 200 mg/m² (days 1–5, 23 days off, total of 18 cycles). The medication was then tolerated well under symptomatic treatment of the side effects. The patient remained in a good condition and without tumor recurrence. The patient's growth developed according to the 50th percentile; clinically, a discreet kyphosis without scoliosis in the functional position and a slight difference in the length of the legs (1.5 cm) was noted. Progression-free follow-up is now 4 years.

Discussion

Anaplastic primary intramedullary spinal cord GGs are extremely rare. An extensive literature research revealed only 4 more pediatric and 4 adult patients (table 1).

The clinical presentation and the imaging studies in the present patient, as well as those in the literature, differ little from the experience with children with more common spinal cord tumors. This patient had presented with a history of motor regression and subsequent significant paraparesis, which is a common finding for spinal cord tumors in children [13]. MRI showed an enhancing intramedullary tumor appearing much like the frequently seen pilocytic astrocytoma [13]. At surgery, the tumor again appeared rather like the common low-grade tumor found in children, and complete removal was not more or less difficult than in such cases.

However, neuropathologic examination revealed a GG with unusual features indicating a higher grade and fulfilling the criteria for an anaplastic variant (WHO III). The absence of findings in favor of a pilocytic astrocytoma, like Rosenthal fibers or eosinophilic granular bodies, in combination with mitotic activity, vascular proliferation and focal necrosis are strong arguments in favor of an anaplastic process [4].

This surprising finding resulted in extensive discussions about the further treatment plan. Usually, complete resection of low-grade tumors in children results in a favorable long-term oncologic outcome [14] and a favorable neurologic outcome when motor pathways remain intact [15]. However, the few anecdotal precedents of this rare tumor variant provided some evidence for an unfavorable outcome with surgical resection followed by either radio- or chemotherapy [1, 4–9]. There is only one report of a long-term survivor in the pediatric population (table 1, gray shading), and this patient received combined adjuvant radiochemotherapy treatment [4]. Therefore, combined treatment with percutaneous irradiation and adjuvant concomitant chemotherapy with temozolomide was planned based on this case report and some prior evidence concerning treatment of low- and high-grade spinal cord astrocytomas [4, 16, 17].

The patient's further neurologic outcome was favorable with a practically complete neurologic recovery, as evidenced by normal physical activities. Oncologic outcome was equally favorable, with a 4-year clinical and radiographic progression-free survival, and thus this case differs from most prior reports (table 1).

Four other case reports of pediatric primary spinal aGG were found in the literature, as follows: one compa-

Table 1. Summary of the literature review for spinal aGG

Patients n	Reference	Age at diagnosis years	Gen- der	Initial symptoms	Localization	Histological diagnosis	STX	CTX	RTX	Comment	Outcome
<i>Pediatric patients with primary spinal aGG (4 patients)</i>											
2	Karremann et al. 2009 [4]	10	F	not reported	spinal (level not specified)	primary aGG	total	yes	54 Gy	consolidation therapy discontinued after 11 months	stable disease after 61 months
		10	M	bladder dysfunction, back pain	spinal (level not specified)	primary aGG	total	yes	no	leptomeningeal spread 1 month after surgery	progressive disease after 7 months
1	Lang et al. 1993 [11]	n.a.	n.a.	back pain and motor weakness	spinal (level not specified)	primary aGG	total	n.a.	n.a.	1 patient with aGG in a series of 30 pediatric spinal GGs	n.a.
1	Karabekir et al. 2006 [9]	2	F	paraparesis, bladder dysfunction	T9-L3	primary aGG	partial	no	40 Gy	postoperative right leg palsy	progression free for 22 months
<i>Adult patients with primary spinal aGG (4 patients)</i>											
1	Bevilacqua et al. 1979 [5]	78	M	spastic paraparesis, sensory deficit	T3-T6	primary aGG	yes	no	yes	rapid neurological deterioration after 5 years	fatal after 9 years (pulmonary embolism)
1	Chrétien et al. 2007 [6]	42	M	paraparesis, sensory deficit	T4	primary aGG	total	n.a.	yes	leptomeningeal spread 12 months after surgery	fatal after 12 months
1	Kitano et al. 1987 [10]	19	F	scoliosis	spinal (level not specified)	primary aGG	n.a.	n.a.	n.a.	postmortem diagnosis	fatal
1	Rodewald et al. 1987 [12]	17	M	bladder dysfunction, leg weakness	L1	primary aGG	partial	n.a.	n.a.	patient suffering from fragile X syndrome	n.a.
<i>Secondary (malignant transformation) and metastatic spinal aGG (7 patients, pediatric and adult)</i>											
1	Di Patre et al. 2004 [7]	42	F	paraparesis, bladder dysfunction	1. T7-T9 2. T5-T10 at 18 months	1. low-grade GG 2. secondary aGG	1. total 2. total	1. no 2. no	1. no 2. 36 Gy	2nd operation for recurrence as aGG after 18 months	paraplegic sub-T5 after the second operation
4 ^a	Blümcke et al. 2002 [3]	35 (mean)	n.a.	n.a.	spinal (level not specified)	metastatic aGG ^a	yes	n.a.	n.a.	22% spinal tumor occurrence in 17 patients with aGG	n.a.
1	Jay et al. 1997 [8]	15	M	seizure	1. right temporal 2. residual tumor at 1 year 3. spinal metastasis at 2 years	low-grade cerebral GG in all 3 tissue samples but unusual karyotype	1. partial 2. total 3. biopsy	1. no 2. no 3. yes	no	tumor lacking classic anaplastic histologic features but showing unusual karyotype	progression free for 5 months after chemotherapy
1	Nakajima et al. 1998 [1]	7	F	headache, nausea, visual disturbance	1. parietal right 2. spinal metastasis at 3 months	metastatic aGG	1. partial 2. no	1. no 2. yes	1. 51 Gy 2. 20 Gy (spine)	leptomeningeal spread 3 months after surgery	fatal after 15 months

The gray shading indicates a patient with a comparable outcome to this case report. STX = Surgical therapy; CTX = chemotherapy; RTX = radiotherapy; n.a. = information not available from the text.

^a Interpretation of the text and percentages mentioned but no information on the individual patient.

rable to the patient presented here with stable disease at 61 months after diagnosis but no information about her clinical status (table 1, gray shading) [4]; one patient with postoperative right leg palsy and a progression-free follow-up of 22 months [9]; one with progressive disease after 7 months [4], and one without information regarding outcome (high-grade tumor in a series of cerebral and spinal low-grade GGs that was not further discussed) [11]. In adult patients, 4 descriptions of primary intramedullary aGG were found [5, 6, 10, 12]. Spinal dissemination of a primary cerebral aGG or malignant transformation of a low-grade GG to aGG was described in 7 patients, including adults and children (table 1) [1, 3, 7, 8].

Karremann et al. [4] report one pediatric patient with stable disease at 61 months, a clinical course comparable to that of the patient reported here. After gross total resection of the tumor, this long-term survivor also received a combination of radio- and chemotherapy. Unfortunately, the authors give no information about the clinical status of this patient [4].

The other patient in the series of Karremann et al. [4] had a less favorable outcome. Gross total resection was achieved, and adjuvant chemotherapy was given but no radiotherapy. Leptomeningeal dissemination was diagnosed in this patient 1 month after surgery, and clinical progression occurred at 7 months [4].

Karabekir et al. [9] describe a partial tumor resection with postoperative right leg weakness in their patient. Radiotherapy of 40 Gy was given, and stable disease (residual tumor) with a persistent neurological deficit were documented 22 months postoperatively [9].

Lang et al. [11] report a series of GGs, cerebral and spinal, but give no specific description of the course of their single patient with primary spinal aGG. Their recommendation is to perform best possible surgery with close clinical follow-up, keeping radio- or chemotherapy as an option for recurrence. However, these data date back over 20 years, and the recommendation for observation refers mainly to the low-grade GGs [11].

In 3 of the 4 case descriptions of primary spinal aGG in adult patients, the outcome was fatal due to tumor-related complications [5, 6, 10]. The fourth adult patient suffered from fragile X syndrome and primary aGG. There is no information available on the clinical course of this patient [12].

Spinal metastasis of a primary cerebral aGG is reported in 5 cases. Blümcke et al. [3] found spinal manifestations in 22% of their patients diagnosed with aGG, while Nakajima et al. [1] give a description of a patient with an

unfavorable clinical course after spinal leptomeningeal spread of a cerebral aGG 3 months after diagnosis.

An interesting feature of GG is described by Di Patre et al. [7] and Jay et al. [8]. In their patients, a primary low-grade GG seemed to undergo malignant transformation or show evidence of malignancy in its clinical behavior. The patient reported by Di Patre et al. [7] suffered a high-grade local recurrence of an initially low-grade spinal GG with severe neurologic impairment after the second operation. Jay et al. [8] give a description of a cerebral GG without evidence of malignancy in the histologic features of 3 consecutive tissue samples (2 cranial, 1 spinal). Despite that finding, spinal metastasis was diagnosed 2 years after the initial operation. Cytogenetic evaluation of the tissue showed an unusual karyotype of this low-grade GG. The patient received chemotherapy after the third operation and remained progression free for 5 months [8].

Conclusion

The neurosurgical concept of complete resection of an intramedullary spinal cord tumor with best possible functional preservation is valid also in the context of primary spinal aGG. This approach, in combination with aggressive adjuvant treatment with both radio- and chemotherapy, was oncologically and neurologically successful in our patient, now with 4 years of progression-free follow-up. Considering the extreme rarity of intramedullary aGG, this anecdotal report may serve as a blueprint for others confronted with the same therapeutic choices and challenges.

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References

- 1 Nakajima M, Kidooka M, Nakasu S: Anaplastic ganglioglioma with dissemination to the spinal cord: a case report. *Surg Neurol* 1998;49:445–448.
- 2 Luyken C, Blumcke I, Fimmers R, Urbach H, Wiestler OD, Schramm J: Supratentorial gangliogliomas: histopathologic grading and tumor recurrence in 184 patients with a median follow-up of 8 years. *Cancer* 2004; 101:146–155.

- 3 Blümcke I, Wiestler OD: Gangliogliomas: an intriguing tumor entity associated with focal epilepsies. *J Neuropathol Exp Neurol* 2002; 61:575–584.
- 4 Karremann M, Pietsch T, Janssen G, Kramm CM, Wolff JE: Anaplastic ganglioglioma in children. *J Neurooncol* 2009;92:157–163.
- 5 Bevilacqua G, Sarnelli R: Ganglioglioma of the spinal cord. A case with a long survival. *Acta Neuropathol* 1979;48:239–242.
- 6 Chrétien F, Djindjian M, Caramelle P, Ricolfi F, Christov C: A 42-year-old man with a densely vascular spinal mass. *Brain Pathol* 2007;17:119–121.
- 7 Di Patre PL, Payer M, Brunea M, Delavelle J, De Tribolet N, Pizzolato G: Malignant transformation of a spinal cord ganglioglioma – case report and review of the literature. *Clin Neuropathol* 2004;23:298–303.
- 8 Jay V, Squire J, Blaser S, Hoffman HJ, Hwang P: Intracranial and spinal metastases from a ganglioglioma with unusual cytogenetic abnormalities in a patient with complex partial seizures. *Childs Nerv Syst* 1997;13:550–555.
- 9 Karabekir HS, Balci C, Tokyol C: Primary spinal anaplastic ganglioglioma. *Pediatr Neurosurg* 2006;42:374–378.
- 10 Kitano M, Takayama S, Nagao T, Yoshimura O: Malignant ganglioglioma of the spinal cord. *Acta Pathol Jpn* 1987;37:1009–1018.
- 11 Lang FF, Epstein FJ, Ransohoff J, Allen JC, Wisoff J, Abbott IR, Miller DC: Central nervous system gangliogliomas. 2. Clinical outcome. *J Neurosurg* 1993;79:867–873.
- 12 Rodewald L, Miller DC, Sciorra L, Barabas G, Lee ML: Central nervous system neoplasm in a young man with Martin-Bell syndrome – fra(X)-XLMR. *Am J Med Genet* 1987;26:7–12.
- 13 Constantini S, Houten J, Miller DC, Freed D, Ozek MM, Rorke LB, Allen JC, Epstein FJ: Intramedullary spinal cord tumors in children under the age of 3 years. *J Neurosurg* 1996;85:1036–1043.
- 14 Constantini S, Miller DC, Allen JC, Rorke LB, Freed D, Epstein FJ: Radical excision of intramedullary spinal cord tumors: surgical morbidity and long-term follow-up evaluation in 164 children and young adults. *J Neurosurg* 2000;93:183–193.
- 15 Kothbauer KF, Deletis V, Epstein FJ: Motor-evoked potential monitoring for intramedullary spinal cord tumor surgery: correlation of clinical and neurophysiological data in a series of 100 consecutive procedures. *Neurosurg Focus* 1998;4:e1.
- 16 McGirt MJ, Goldstein IM, Chaichana KL, Tobias ME, Kothbauer KF, Jallo GI: Extent of surgical resection of malignant astrocytomas of the spinal cord: outcome analysis of 35 patients. *Neurosurgery* 2008;63:55–60.
- 17 Kim WH, Yoon SH, Kim CY, Kim KJ, Lee MM, Choe G, Kim IA, Kim JH, Kim YJ, Kim HJ: Temozolomide for malignant primary spinal cord glioma: an experience of six cases and a literature review. *J Neurooncol* 2011; 101:247–254.