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Case Report

A case of adult anaplastic cerebellar ganglioglioma

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Abstract

Background: Anaplastic posterior fossa ganglioglioma in adults is exceedingly rare. To date, only one case of adult anaplastic posterior fossa ganglioglioma has been reported in the English literature and none has been described at the cerebellum. To our knowledge, this report is the third case of malignant posterior fossa ganglioglioma in adults and the first at the cerebellum. In general, this entity can be misdiagnosed preoperatively as a primary posterior fossa neoplasm, and by reporting our clinical and radiographic observations we want to add to the existing literature on this rare entity.

Case Description: A 40-year-old man presented with a history of headaches and dizziness and progressive gait disturbance and was diagnosed with anaplastic ganglioglioma in the posterior fossa.

Conclusions: Although rare, our case demonstrates that anaplastic ganglioglioma should be considered in the differential diagnosis of infratentorial tumors in adult patients.

Key Words: Anaplastic ganglioglioma, cerebellum, posterior cranial fossa, prognosis

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INTRODUCTION

Anaplastic ganglioglioma is a very infrequent primary neoplasm of the central nervous system. These tumors are most commonly found in the supratentorial compartment, and any occurrence in the posterior fossa is considered a rare event.[20]

To date, only few cases of malignant infratentorial gangliogliomas have been documented, and commonly among children.[6] Only one other case of anaplastic posterior fossa ganglioglioma in an adult patient has been reported in the English literature.[6]

Here, we report an adult patient with anaplastic ganglioglioma of the cerebellum; the first such reported case in the literature. We also review the literature related to infratentorial malignant gangliogliomas, and discuss the clinical manifestations, imaging and histopathological findings, reported treatments, and the outcome associated with such lesions.

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CASE REPORT

A comprehensive literature search for this review was conducted on PubMEd, MedLine, and Google Scholar. There were no limitations on the date, type, or language of the publication. The first search was conducted using the term "posterior fossa ganglioglioma" followed by "posterior fossa anaplastic ganglioglioma," "cerebellar anaplastic ganglioglioma," and "posterior fossa ganglioblastoma."

The titles and abstracts were reviewed and only11 publications were selected relating to malignant posterior fossa ganglioglioma; 3 in adults and 8 in children. These cases are reviewed in Table 1.

CASE DESCRIPTION

A 40-year-old man presented to the neurosurgical department with a history of headache for 3 months. His headache was associated with a progressive staggering gait, dizziness, and nausea. Past and family history was unremarkable.

General physical examination and review of systems were not contributory. Routine blood tests were normal, and chest X-ray was normal. The patient was HIV-negative. Neurological examination showed focal cerebellar signs, including ipsilateral cerebellar ataxia, and slurred speech. The fundus oculi were normal bilaterally.

Cranial magnetic resonance imaging (MRI) revealed a solid mass with a maximum diameter of 3 cm, which appeared hypointense on T1-weighted sequences and hyperintense on T2-weighted images. The lesion enhanced irregularly after the administration of intravenous gadolinium. MR spectroscopy was obtained and showed a high choline/creatine ratio with increased myoinositol level, suggesting anaplastic behavior of the lesion [Figure 1].

Under a working diagnosis of a neoplastic process, a standard suboccipital craniotomy was performed in the prone position. After opening the dura mater and performing a corticectomy for access and after transvermian approach, the lesion was found to be infiltrative and hypervascular. Complete tumor resection was performed, as shown in the postoperative CT scan. The postoperative course was uneventful. The histological diagnosis of the lesion yielded an anaplastic ganglioglioma, with the tumor showing biphasic pattern of ganglion cells and neoplastic glial cells. The malignant glial component characterized by hypercellularity, nuclear atypia, and increased mitotic activity; however, no microvascular proliferation or necrosis was present [Figure 2a]. The neoplastic glial cells were immunoreactive for glial fibrillary acidic protein (GFAP), immunoreactive for synaptophysin, and the Ki67 proliferation index was 20% [Figure 2b].

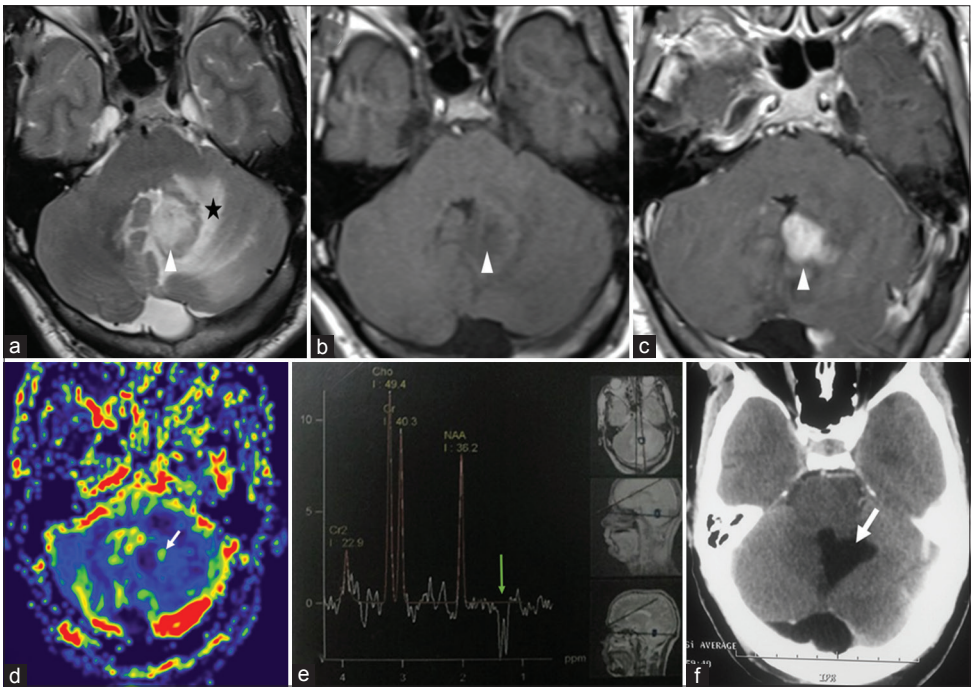

Figure 1: Preoperative magnetic resonance imaging (MRI). T2 (a), T1 native (b), and T1 after gadolinium administration (c): left cerebellar lesion (arrowhead) slightly hypointense on T1-weighted images and hyperintense on T2-weighted images, with peritumoral edema (black star) and strong ill-defined contrast enhancement. (d) MR perfusion with cerebral blood volume (CBV) cartography: slight peripheral hyperperfusion (white arrow); rCBV = 1.9 × normal contralateral cerebellum white matter. (e) Proton MR spectroscopy: elevated doublet of lactate at 1.33 ppm which is inverted on the spectrum with long echo-time (green arrow). NAA/Creatine ratio is reduced (f) Postoperative CT scan: resection cavity (white arrow)

Table 1: Summary of the reported cases of malignant posterior fossa ganglioglioma

References	Age at diagnosis (years)	Sex	Initial symptoms	Location	Histological diagnosis	Imaging studies	Therapy	Outcome
Hirose *et al*. 1992	12	F	headache, gait disturbance and right hemiplegia	right cerebellar peduncle, medulla oblongata and upper cervical spinal cord	Grade III ganglioglioma: anaplastic ganglioglioma	Gadolinium-enhanced T1-weighted: irregularly gadolinium-enhancing areas	Partial resection	Died 8 months
Jay V *et al*. 1994	10	M	seizures, headaches, vomiting, and progressive right hemiparesis	left cerebral peduncle	Grade III ganglioglioma: anaplastic ganglioglioma	hyperintense in T2	Subtotal removal and radiation	Not reported
Jay V *et al*. 1997	15	M	seizures	The right mesial temporal lobe superior vermian folia with widespread leptomeningeal spread	Grade III ganglioglioma: anaplastic ganglioglioma	Gadolinium-enhanced T1-weighted	Subtotal removal and chemotherapy	Recurrence after 2 years
Takei *et al*. 2007	7	M	developmental delay, increased cranial pressure	the cerebellar vermis and paramedian cerebellar hemispheres	Grade III ganglioglioma: anaplastic ganglioglioma	large nonhomogeneous mass lesion (low isointensity on T1-weighted images and high intensity on T2-weighted images	Subtotal removal and radiation	Stable disease after 5 months
Karremann *et al*. 2009	14	M	Vomiting, ataxia	Pons and 4th ventricle	Grade III ganglioglioma: anaplastic ganglioglioma	Not mention	Subtotal removal and radiation	Stable disease after 8 months
Shah *et al*. 2012	14	M	nausea, vomiting and headache	the fourth ventricle	Grade III ganglioglioma: anaplastic ganglioglioma	irregular strong enhancingmass on gadolinium-enhanced T1-weighted	Subtotal removal and radiation	Stable disease after 18 months
Zanello *et al*. 2016	7	M	increased cranial pressure	right cerebellar peduncle	Grade III ganglioglioma: anaplastic ganglioglioma	contrast-enhanced cystic lesion	Total resection and radiochemotherapy	Stable disease after 34 months
Lüdemann *et al*. 2017	11	M	headache and double vision	quadrigeminal plate	Grade III ganglioglioma: anaplastic ganglioglioma	homogenously in contrast enhancing and hyperintense in T-2 weighted imaging	Surgical partial removal and radiochemotherapy	Stable disease after 3 months
Matzusaki *et al*. 2005	64	F	dizziness	Right cerrebello-pontine angle	Grade IV ganglioglioma: ganglioblastoma	Mixed intensity on T1 and T2 MRI, cystic enhancing Cerebello pontine angle mass	Subtotal removal and radiation	Died 12 months after diagnosis
Mekni *et al*. 2006	25	F	intracranial pressure	cerebellar	Grade IV ganglioglioma: ganglioblastoma	Cystic enhancing cerebellar mass on CT	Subtotal removal radiation	(60Gy in 30 daily fractions for 5 weeks

Contd...

Table 1: Contd...

References	Age at diagnosis (years)	Sex	Initial symptoms	Location	Histological diagnosis	Imaging studies	Therapy	Outcome
González Toledo *et al*. 2012	33	M	Right sided weakness and headaches	Brainstem	Grade III ganglioglioma: anaplastic ganglioglioma	hypointense on T1 and hyperintense in T2 and FLAIR with cystic and solid components	biopsy	Not reported
Present case	40	M	Headaches and progressive staggering gait	cerebellum	Grade III ganglioglioma: anaplastic ganglioglioma	hypointense on T1 and hyperintense in T2	Subtotal removal and radiation total dose: 54 Gy, (1.8 Gy per day, 5 days a week)	Died 10 months after diagnosis

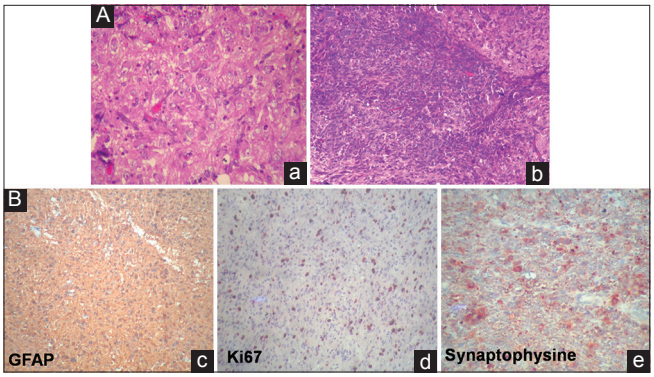

Figure 2: (A): (Hematoxylin eosin ×20): tumor showing biphasic pattern of ganglion cells and neoplastic glial cells. (b): (Hematoxylin eosin ×20): malignant glial component characterized by hypercellularity, nuclear atypia and increased mitotic activity. (B) Immunohistochemistry ×400. (c) GFAP: the neoplastic glial cells are immunoreactive for GFAP. (d) Ki67: Ki67 proliferation index was 20%. (e) Synaptophysin: the neoplastic ganglion cells are immunoreactive for synaptophysin

The patient received standard fractionated radiotherapy at a total dose of 54 Gy (1.8 Gy per day, 5 days a week) for 6 weeks. Follow-up of the patient with a computed tomography (CT) scan for 6 months after the surgery did not show any evidence of tumor recurrence [Figure 2f]. Clinically, the patient showed only a persistent mild gait abnormality (truncal ataxia) but no other neurological abnormalities.

Despite two cycles of adjuvant temozolomide, the tumor recurred and progressed with cerebellar multiple nodular location and died 10 months after the surgery.

Only 3 cases of malignant posterior fossa ganglioglioma in adults have been reported in the English literature (A summary of patient characteristics at presentation and surgical outcome is presented in Table 1). Only Toledo *et al*. described a Grade III ganglioglioma of the brainstem.[6] WHO grade IV ganglioglioma or ganglioblastoma had been described by Matzusaki *et al*. and Mekni *et al*., one at the cerebellopontine angle and the second as a cerebellar ganglioblastoma.[12,13]

DISCUSSION

Gangliogliomas are rare mixed glioneuronal tumors that represent less than 1% of central nerve system neoplasms[11,14,26] and contain a mixture of neoplastic glial and neuronal cells.[2,18,26]

Gangliogliomas are staged according to the most recent WHO classification[5] with WHO grades I and II representing benign tumors and accounting for 90–98% of ganglioglioma cases. The remaining cases are composed of anaplastic gangliogliomas (WHO grade III) and ganglioblastomas (WHO grade IV), which are rare and poorly characterized.[5,11,21] Their incidence is estimated at approximately 0.02 cases per million people per year.[19,23]

While the exact etiology and pathogenesis remains unclear, the cell of origin is thought to be a glioneuronal precursor.[11] The glial component represents the malignant portion of the tumor in a majority of the cases, but transformation has also been reported in the neural component, and neuroblastomatous ganglioglioma have been described.[11,21]

To be considered an anaplastic ganglioglioma, the tumor had to have five or more mitoses per 10 high-power fields, and at least one of the additional criteria, angiogenesis and/or necrosis, in the glial component.[26]

Anaplastic ganglioglioma can arise *de novo* or secondary via malignant transformation of a pre-existing WHO grade I ganglioglioma. The rate of intracranial gangliogliomas malignant transformation has been calculated to range from 0.6 to 14.5%.[15,25]

Only 11 infratentorial anaplastic ganglioglioma cases have been reported in the literature that are preferentially diagnosed in children with a slight preponderance among males.[6-10,13,16,17,22,26] These anaplastic gangliogliomas are rare tumors whose epidemiology, natural history, prognostic factors, and treatment options have been sparsely documented thus far. To date, only 3 cases of

malignant posterior fossa ganglioglioma in adults have been reported in the English literature [Table 1].[6,16,17] González Toledo *et al*. described a Grade III ganglioglioma of the brainstem in a 33-year-old man. WHO grade IV ganglioglioma or ganglioblastoma have been described by Matzusaki *et al*. in a 64-year-old woman with a cerebellopontine angle ganglioblastoma[16] and Mekni *et al*. in a 25-year-old woman with a cerebellar ganglioblastoma.[17]

There have been no previous reports describing an anaplastic ganglioglioma (grade III) located in the parenchyma of the cerebellum.

Our review of the literature describing gangliogliomas of the posterior fossa has yielded that these tumors can manifest similar to other lesions in this location with hydrocephalus, cranial nerve palsies, gait and speech disorders, and even myoclonus.[3] In our patient, preoperative symptoms included headache associated with progressive staggering gait, dizziness, and nausea. Cerebellar signs including cerebellar ataxia and slurred speech were noted.

The median history of disease reported by Karremann *et al*. was 9 months (range, 1.0–43.0 months) and depended on the location and size of the tumor.[10]

In a majority of the series and reported cases, the characteristics described on MRI were hypointensity in T1, hyperintensity on T2 and FLAIR, and patchy enhancement after contrast administration. The apparent diffusion coefficient value of anaplastic ganglioglioma was reported to be reduced (0.95×10^{-3} mm^2/s (SD = 0.053), which likely reflects its high cellularity. In gangliogliomas with anaplastic features, MR spectroscopy has been previously shown do demonstrate peaks of glutamate, choline, and myoinositol.[6] In our case, the choline peak was high and the myoinositol was pronounced.

Due to their low frequency, a standard treatment for anaplastic ganglioglioma has not been established yet. According to the literature, complete surgical resection is recommended.[10]

Following resection, radiotherapy seems to improve local control rates in high-grade gangliogliomas and should be applied as an adjuvant therapy. Standard fractionated radiotherapy (54.0–59.4 Gy total dose; doses of 1.8 Gy/day, 5 days/week over 6–7 weeks) was common for most cases.[10,12]

The role of systemic chemotherapy has not been established in prospective randomized trials due to low number of cases seen, and previously employed regimen are not well documented in the existing case series. Prognostic factors of poor survival are older age at diagnosis, male sex, and malignant glial features.[23]

Anaplastic gangliogliomas appear to represent a very aggressive disease with poor overall outcome (median progression-free survival, 10 months; median overall survival; 27 months).[26] Our patient survived 10 months after total resection with radiation.

Varlet *et al*. have shown that the extent of surgical resection in malignant glioneuronal tumors is significantly correlated to survival.[24] In their cohort of 40 mixed cases, median survival was 44 months in patients who underwent gross total resection but only 15 months in those who underwent subtotal resection.[24] It is also known that these tumors can rarely form distant extracranial metastases,[4] which may require surveillance scanning for staging during follow-up.

In a recent study, immunohistochemical molecular analyses indicated that *BRAF V600E* mutation is present in 39% of anaplastic gangliogliomas in both glial and neuronal population without prognostic significance.[26]

Personalized therapies as anti-BRAF inhibitors can be a useful adjuvant therapy together with the first-line oncological treatments, and a few cases of anaplastic gangliogliomas treated by anti-BRAF therapy with promising results have been reported.[1,26]

CONCLUSION

We present a rare case of anaplastic ganglioglioma WHO III in the cerebellum of an adult patient along with its clinical diagnosis and treatment. This is only one of a few such cases observed thus far and contributes to our understanding of the characteristics of this rare posterior fossa tumor. The present work demonstrates that anaplastic ganglioglioma need to be considered in the differential diagnosis of malignant primary infratentorial brain tumors in adult patients.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Bautista F, Paci A, Minard-Colin V, Dufour C, Grill J, Lacroix L, *et al*. Vemurafenib in pediatric patients with BRAFV600E mutated high-grade gliomas. Pediatr Blood Cancer 2014;61:1101-3.
2. Dahiya S, Haydon DH, Alvarado D, Gurnett CA, Gutmann DH, Leonard JR. BRAFV600E mutation is a negative prognosticator in pediatric ganglioglioma. Acta Neuropathol 2013;125:901-10.
3. De Souza RB, de Aguiar GB, Araújo JLV, Mayrink D, dos Santos ARL, *et al*. Posterior fossa ganglioglioma: An unusual neoplasm in a rare location. Austin Neurosurg Open Access 2014;1:1010.
4. Erguvan-önal R, Önal Ç, Aydin NE. Anaplastic Ganglioglioma: Is it a Sign of Better Prognosis? J Nervous Sys Surg 2009;2:72-8.
5. Gelabert-González M, Amo JM, Arcos Algaba A, Serramito García R, Castro Bouzas D, Díaz Cabana L, *et al*. Gangliogliomas intracraneales. Revisión de una serie de 20 pacientes. Neurología 2011;26:405-15.
6. González Toledo E, Nader M, Thomas-Ogunniyi J, Wilson J. Anaplastic Ganglioglioma of the Brainstem in an Adult. Neuroradiol J 2012;25:325-9.
7. Hirose T, Kannuki S, Nishida K, Matsumoto K, Sano T, Hizawa K. Anaplastic

ganglioglioma of the brain stem demonstrating active neurosecretory features of neoplastic neuronal cells. Acta Neuropathol 1992;83:365-70.
8. Jay V, Squire J, Becker LE, Humphreys R. Malignant transformation in a ganglioglioma with anaplastic neuronal and astrocytic components. Report of a case with flow cytometric and cytogenetic analysis. Cancer 1994;73:2862-8.
9. 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;13:550-5.
10. Karremann M, Pietsch T, Janssen G, Kramm CM, Wolff JE. Anaplastic ganglioglioma in children. J Neurooncol 2009;92:157-63.
11. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, *et al.* The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A summary. Acta Neuropathol 2016;131:803-20.
12. Lucas JT, Huang AJ, Mott RT, Lesser GJ, Tatter SB, Chan MD. Anaplastic ganglioglioma: A report of three cases and review of the literature. J Neurooncol 2015;123:171-7.
13. Lüdemann W, Banan R, Hartmann C, Bertalanffy H, Di Rocco C. Pediatric intracranial primary anaplastic ganglioglioma. Childs Nerv Syst 2017;33:227-31.
14. 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;101:146-55.
15. Majores M, von Lehe M, Fassunke J, Schramm J, Becker AJ, Simon M. Tumor recurrence and malignant progression of gangliogliomas. Cancer 2008;113:3355-63.
16. Matzusaki M, Uno M, Kageji T. Anaplastic ganglioglioma of the cerebellopontine angle. Neurol Med Chir (Tokyo) 2005;45:591-5.
17. Mekni A, Chelly I, Haouet S, Zitouna M, Kchir N. Malignant cerebellar ganglioglioma. A case report and review of the literature. Neurochirurgie 2006;52:119-22.
18. Prabowo AS, Iyer AM, Veersema TJ, Anink JJ, Schouten-van Meeteren AY, Spliet WG, *et al.* BRAF V600E mutation is associated with mTOR signaling activation in glioneuronal tumors. Brain Pathol 2014;24:52-66.
19. Selvanathan SK, Hammouche S, Salminen HJ, Jenkinson MD. Outcome and prognostic features in anaplastic ganglioglioma: Analysis of cases from the SEER database. J Neurooncol 2011;105:539-45.
20. Shah MJ, Sircar R, Linder-Luch M, Böhm J, van Velthoven-Wurster V. Anaplastic Posterior Fossa Ganglioglioma in a Child: Case Report and Short Review of the Literature. J Neurol Surg A 2012;73:46-9.
21. Siddique K, Zagardo M, Gujrati M, Olivero W. Ganglioglioma presenting as a meningioma: Case report and review of the literature. Neurosurgery 2002;50:1133-5.
22. Takei H, Dauser R, Su J, Chintagumpala M, Bhattacharjee MB, Jones J, *et al.* Anaplastic ganglioglioma arising from a Lhermitte-Duclos-like lesion. Case report. J Neurosurg 2007;107:137-42.
23. Terrier LM, Bauchet L, Rigau V, Amelot A, Zouaoui S, Filipiak I, *et al.* Natural course and prognosis of anaplastic gangliogliomas: A multicenter retrospective study of 43 cases from the French Brain Tumor Database. Neuro Oncol 2016;30:186.
24. Varlet P, Soni D, Miquel C, Roux FX, Meder JF, Chneiweiss H, Daumas-Duport C. New variants of malignant glioneuronal tumors: A clinicopathological study of 40 cases. Neurosurgery 2004;55:1377-91.
25. Yust-Katz S, Anderson MD, Liu D, Wu J, Yuan Y, Olar A, *et al.* Clinical and prognostic features of adult patients with gangliogliomas. Neuro-Oncol 2014;16:409-13.
26. Zanello M, Pages M, Tauziède-Espariat A, Saffroy R, Puget S, Lacroix L, Dezamis E, *et al.* Clinical, Imaging, Histopathological and Molecular Characterization of Anaplastic Ganglioglioma. J Neuropathol Exp Neurol 2016;75:971-80.