

# Pediatric primary anaplastic ganglioglioma with malignant neuronal component

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Gangliogliomas (GGs) represent approximately 0.4%-1.0% of all brain tumors. Anaplastic gangliogliomas (AGGs) form 5-10% of all GGs. They are a mixed neuronal-glial tumor of central nervous system and composed by two cell lines; neuronal (ganglionic) and glial cells. Anaplastic component of AGGs is usually glial cells. Malignant neuronal component is a rare condition. Here we report an 8-year-old male patient who was diagnosed with primary AGG with malignant neuronal component and was treated with surgery, adjuvant radiotherapy and chemotherapy.

**Key words:** anaplastic ganglioglioma, malignant neuronal component, pediatrics.

Gangliogliomas (GGs) are very rare tumors of the central nervous system (CNS). They are classified under the “neuronal and mixed neuronal-glial tumors of CNS” according to the 2016 World Health Organization (WHO) classification of CNS tumors.<sup>1</sup> They represent approximately 0.4%-1.0% of all brain tumors.<sup>2,3</sup> Histopathologically they are composed of ganglionic and glial cells. They are thought to arise from glioneuronal precursor cells that are capable of differentiation to both glial and neuronal cells.<sup>4</sup> Gangliogliomas are grade I tumors but anaplastic gangliogliomas (AGGs) are grade III tumors and they form 5-10% of all GGs.<sup>5</sup> Although anaplastic transformation of neuronal component is reported in some cases,<sup>6-10</sup> their anaplastic component is usually glial cells.<sup>5</sup> They have been described as primary or secondary neoplasms (progression of previously low grade ganglioglioma).<sup>11</sup>

Anaplastic gangliogliomas can occur anywhere throughout the CNS but they occur mostly in the supratentorial region and especially in the temporal lobe of the brain.<sup>11</sup> These tumors are very epileptogenic; they are mostly seen in children and young adults, more frequently in males.<sup>5</sup>

Here we report an 8-year-old male patient who was diagnosed with primary AGG with malignant neuronal component and was treated with surgery, adjuvant radiotherapy and chemotherapy.

## Case Report

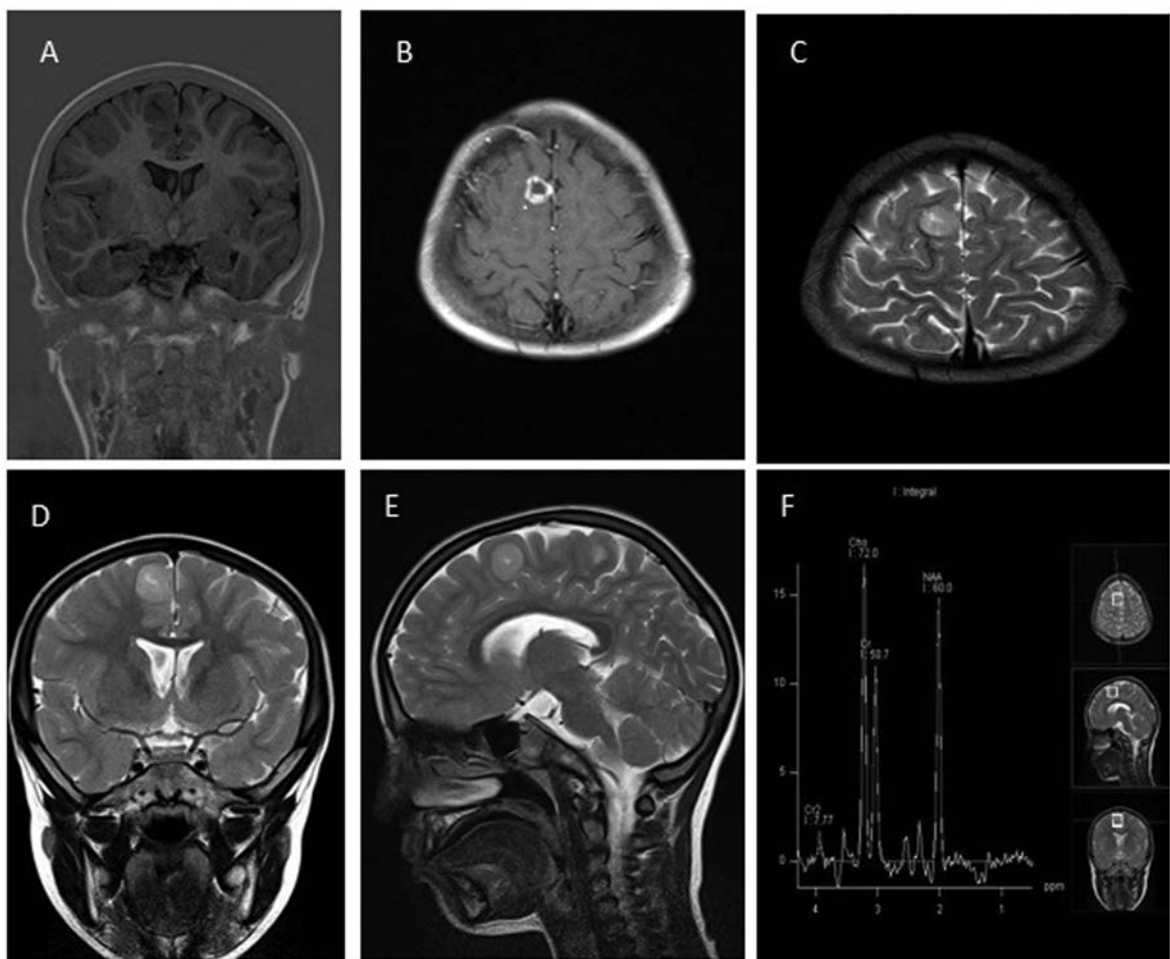
An 8-year-old male patient had been followed with the diagnosis of epilepsy (generalized tonic seizures) for three years. Although he had used antiepileptic drugs regularly, his seizures became more frequent in the last 3 months; his medical history was unremarkable, neurologic examination and electroencephalography were normal. Cranial magnetic resonance imaging (MRI) revealed a solid mass in the right frontal region with a maximum diameter of 15 mm, located at parasagittal cortical-subcortical region, causing expansion at the nearby gyrus, iso/hypointense on T1-weighted sequences and hyperintense on T2-weighted images (Fig. 1A, C, D, E). The lesion showed retention of gadolinium (Fig. 1B). Magnetic resonance spectroscopy showed moderate increase in choline peak (Fig. 1F). The lesion prediagnosed as dysembryoplastic neuroepithelial tumor (DNET) and underwent neurosurgery. With

right frontal craniotomy, after opening the dura intraoperative ultrasonography was performed, correct localization of the tumor was verified. After the brain parenchyma was opened with cortical incision, the yellow-grey tumoral lesion was totally resected. Postoperatively; patient was followed up at the intensive care unit; phenytoin was continued as antiepileptic medication. Neurologic examination was normal. He was discharged at the end of seventh day.

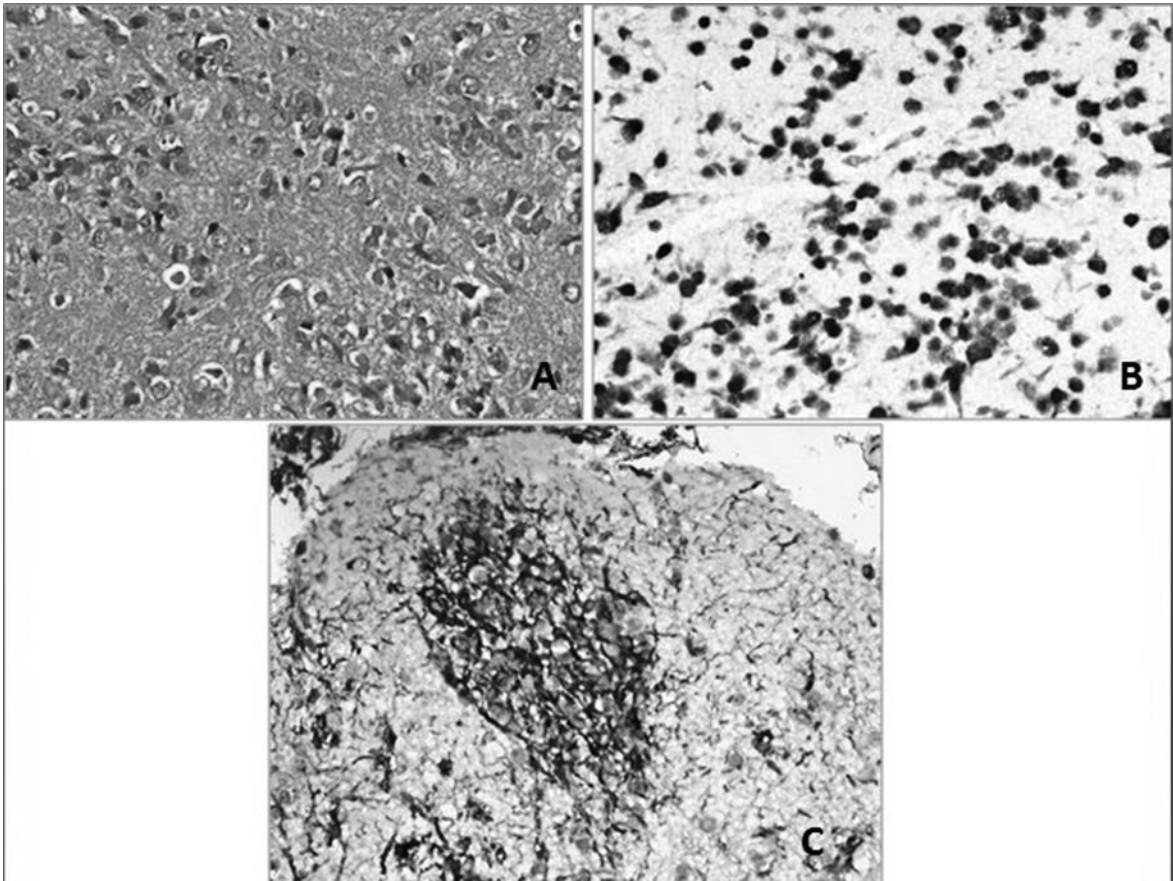
The tumoral tissue was consulted with Pathology Laboratory of Marmara University, Institution of Neurological Sciences. The tumor was composed of two cell lines: glial and neuronal (ganglionic cells) (Fig. 2A, C). The malignant component was neuronal component

and these cells were Neu-N positive (Fig. 2B). Glial component was glial fibrillary acidic protein (GFAP) and synaptophysin positive (Fig. 2C). Ki-67 proliferation index was found to be 20-25%. The tumor was negative for epithelial membrane antigen, neurofilament protein (NFP) and CD34. The diagnosis was malignant glioneuronal tumor, anaplastic ganglioglioma, grade III.

One month after neurosurgery, after his pathologic diagnosis became certain, patient was screened for residual tumor tissue and metastasis to the spinal cord; cerebrospinal fluid cytology was negative, whole spinal MRI was normal. His cranial MRI revealed a 15 mm lesion with thin peripheral contrast enhancement in right frontal parasagittal region



**Fig. 1.** A. The solid mass in the right frontal region with a maximum diameter of 15 mm, located at parasagittal cortical-subcortical region, causing expansion at the nearby gyrus, iso/hypointense on T1-weighted sequences. B: The lesion showed retention of gadolinium. C,D,E: The solid mass looked hyperintense on T2-weighted images in the right frontal region. F: Magnetic resonance spectroscopy showed moderate increase in choline peak.



**Fig. 2.** A. Clusters of atypical ganglionic cells with vesicular nuclei and prominent nucleoli (Hematoxylin and eosin, x400). B: Immunohistochemical expression of NeuN in the nuclei of ganglionic tumor cells (NeuN, x400). C: Immunohistochemical expression of glial fibrillary acidic protein (GFAP) in glial component of the tumor cells (GFAP, x100).

at the neighborhood of interhemispheric fissure and diffusion restriction was not observed. Differentiation of the residual tumoral tissue or postoperative changes could not be done. Radiotherapy (RT) was performed using linear accelerators with conventional fractionation. Eclipse (ver. 8.6; Varian Medical Systems, Inc. Palo Alto, CA, USA) was used as the three-dimensional conformal radiotherapy (3D-CRT) planning software program. Simulation CT images were performed with 3 mm wide slices. The treatment plan for RT was based on coregistered preoperative and postoperative MRI. Radiotherapy was administered using multifield technique, with the patient immobilized in a thermoplastic mask. The patient was treated with local fields including surgical bed plus a 1–2 cm margin to dose of 50 Gy with daily fraction size of 2 Gy. The patient received 10 Gy as a boost after 50 Gy. The total dose for patient treated with conventional fractionation

(2 Gy per fraction) was 60 Gy. The treatment was well tolerated; dexamethasone was used for anti-edema therapy.

We added vincristine (1.5 mg/m<sup>2</sup>/dose) therapy weekly during the radiotherapy (Totally 6 doses). After RT cisplatin and etoposide regimen (Cisplatin: 100 mg/m<sup>2</sup>/day, on day 1, etoposide: 120 mg/m<sup>2</sup>/day, on days 1 to 3),<sup>12</sup> was administered to the patient. Vincristine (1.5 mg/kg/day, on day 1) was added to the chemotherapy protocol. Courses were administered with 4 week intervals. We evaluated the patient at 3 month intervals. A lesion at 11 mm diameter with thin peripheral contrast enhancement in right frontal parasagittal region was continuously seen during the treatment evaluations after 3<sup>th</sup>, 6<sup>th</sup> and 8<sup>th</sup> courses. At a council meeting with representatives from the department of neurosurgery, radiation oncology and pediatric oncology, it was contemplated that the lesion



might be postoperative changes in the brain parenchyma or radiation necrosis and a decision to follow up this lesion was made. Eight courses of chemotherapy were administered. Periodical clinical and radiological evaluations are continuing with 3 month intervals. After 13 months from the finish of the treatment (25 months from the diagnosis), his cranial MRI revealed 11.5 mm diameter stable lesion at right side of the frontal lobe without spinal cord involvement. Written informed consent was obtained from patient's father for this case presentation.

### Discussion

Gangliogliomas (GGs) occur mainly in children and young adults and account for 1-4 % of all CNS tumors of pediatric patients.<sup>13</sup> Anaplastic gangliogliomas are 5-10% of all GGs.<sup>5</sup> They are composed of two cell lines, glial and neuronal cells and they are localized especially temporal lobe of the brain. Patients are usually admitted with seizures, because these tumors are very epileptogenic. Our patient was followed up because of epilepsy too. After his seizures became more frequent, the imaging of the brain revealed a tumor in the right frontal region.

Magnetic resonance imaging findings of AGGs show gadolinium enhanced tumors. Some studies have noted that MR spectroscopy of GGs may reveal distinct but non-specific choline peaks which may differentiate these from benign conditions, but not necessarily from other primary brain tumors.<sup>13</sup> Our patient's MRI findings revealed a solid mass which had retention of gadolinium in the right frontal region (Fig. 1). Magnetic resonance spectroscopy showed moderate increase in choline peak. As in concordance with the literature these findings were thought to be low grade brain tumor (DNET) before the surgery and pathology. For this reason, we believe that these tumors cannot be diagnosed accurately with radiological findings alone; pathological examination must be done for correct diagnosis.

Histopathologically, AGGs are the high-grade tumors that are composed of neuronal and glial cells. Following the WHO criteria, diagnosis of AGGs requires the tumor to be composed of clusters of atypical ganglion cells, with perivascular proliferation, perivascular lymphocytes, or microcalcification.<sup>5</sup> The glial

component more frequently develops anaplasia, with hypercellularity, focal necrosis, increased mitotic activity and microvascular proliferation. The confirmation of the neuronal component might need the immunohistochemical use of synaptophysin, chromogranin, neurofilaments, PGP9.5, NeuN and/or specific neuronal enolase, as well as glial components that might be positive for GFAP and focally for S100.<sup>2</sup> In the literature there are few cases which have anaplastic neuronal component. In two of them there was malignant transformation of GGs to AGGs with the malignant component of neuronal cells,<sup>9,10</sup> and in three there was primary AGGs with malignant neuronal cell component.<sup>6-8</sup> Our case is rare because of the malignant component of this tumor is the neuronal component. Histopathologically glial component of the tumor was GFAP positive (Fig. 2C) and atypical ganglionic cells had vesicular nuclei and prominent nucleoli (Fig. 2A). They were positive for NeuN (Fig. 2B).

Total tumor resection of AGGs is important for better survival.<sup>11,13,14</sup> In the largest evaluation of AGGs outcomes using the Surveillance, Epidemiology, and End Results (SEER) database, 5-year survival was 63% (95 %CI 46-76).<sup>11</sup> The primary prognostic factor was resectability at presentation with a greater than 25% difference in overall survival at 2 years.<sup>11</sup> In a retrospective analysis of 60 patients with high-grade GGs, Rades et al.<sup>15</sup> detected a statistically significant benefit of RT in local control following subtotal resection but no survival benefit. They also found dose escalation beyond 54 Gy improved local control. In the data of SEER<sup>11</sup> RT was not beneficial for survival but they found patients who had adjuvant RT tend to have longer survival than others. One month after the surgery of our patient a lesion with 15 mm in diameter at right frontal region was seen at MRI. This finding could not be differentiated from residual tumoral tissue or postoperative changes, so we gave the patient a total of 60 Gy (10 Gy boost to the lesion and 50 Gy to whole cranium) RT. After radiotherapy and chemotherapy, the lesion diameter decreased to 11.5 mm and this finding has been stable during follow up of the patient.

The role of chemotherapy has not been established in prospective randomized trials

and poorly reported in existing case series. In a series with eight patients, Karreman et al.<sup>13</sup> used the HIT-GBM protocol<sup>16</sup> after surgery and RT. Their 5 year event free survival (EFS) was  $63 \pm 17\%$  and overall survival was  $88 \pm 12\%$ . In a case series by Lucas et al.<sup>17</sup> 3 patients with AGGs experienced leptomeningeal failures, also in Scieocianti et al.'s<sup>18</sup> review of 19 pediatric AGGs, 10 (53%) patients experienced tumor progression and of these, five progressed distantly. In the data of SEER<sup>11</sup> which is the largest series of the literature, adjuvant chemotherapy was not examined as a survival factor because of the limited information about the chemotherapy usage, however, it is thought that chemotherapy may be warranted as an upfront treatment modality on the basis of neuroaxis failure and recurrences. In light of these findings, we gave our patient vincristine during RT and then eight courses of vincristine, cisplatin and etoposide therapy. Our patient did not have any epileptic seizures after the primary surgery, and he has been following during 13 months from the end of the treatment with a stable lesion in 11.5 mm diameter at right side of the frontal lobe without spinal cord involvement.

In summary, our patient was different because of the malignant neuronal component of the primary AGG. In the treatment design of these tumors an efficacious surgery must be included. Adjuvant radiotherapy and chemotherapy might be involved especially in partially resected tumors because of the recurrence and neuroaxis failure of the tumor.

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