CASE REPORT

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# Giant Cell Variant of Glioblastoma Multiforme: Report of a Rare Variant in a Child

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ABSTRACT

Malignant glial tumors are rare in children. Giant cell variant is a rare subtype of glioblastoma, accounting for about 0.8% of brain tumors and 5% of glioblastoma tumors. Giant cell glioblastoma is a male predominant tumor in children and adults. Due to the low prevalence of this variant, available information is limited. An 11-year-old female child was referred with a chief complaint of a progressive persistent headache. MRI showed a well-defined cystic lesion with a solid mural component in the right parietal lobe with a compression effect on the ipsilateral ventricular system. Surgery was done. After the pathologist reported glioblastoma multiforme, a giant cell variant, the patient received 30 sessions of radiation therapy. The patient was readmitted 18 months later with a headache, and the pathologist confirmed the recurrence of the tumor. Based on radiology, the giant cell glioblastoma cannot be distinguished from the common subtype glioblastoma. The pathologists must be aware of this entity, and histologic differential diagnoses are warranted for diagnostic, prognostic, and therapeutic purposes.

**Keywords: Giant cell, Glioblastoma, Child**



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## INTRODUCTION:

Glioblastoma multiforme (GBM) was first described in the 1800s, and Giant cell Glioblastoma (GC-GBM) was first presented in 1979 by Zulch as "monstrocellular sarcoma ". However, the astrocytic nature of this tumor was confirmed with an experimental demonstration of GFAP (Glial Fibrillary Acidic Protein) in giant cells component in 1993. Finally, since 2000, this tumor has been classified according to the World Health Organization (WHO) as grade IV diffuse astrocytic tumor (1, 2). GC-GBM is a rare brain tumor, especially in children, characterized by multinucleated giant cells and bizarre nuclei with increased expression of P53. Despite poorly differentiated astrocytic cells in the microscopic examination, it has a better prognosis than other variants of GBM (3). Here we report a rare variant of GBM in a female child with recurrence in 18 months.

## CASE REPORT:

An 11-year-old female child was brought by his father on January 19, 2019, with a chief complaint of progressive persistent headache since four days ago. The headache was more severe early in the morning. Nausea and vomiting were also present. Progression of headache and left hemiparesis made the patient seek medical care. Brain Computed Tomography (CT) scanning was done, and heterodense lesion measuring 48 x 45mm was noted. The mass had a compressive effect, midline shift, and vasogenic edema that suggested oligodendroglioma. The patient was referred to the pediatric hospital for complementary treatment. Drug and past medical history were unremarkable. The patient was the first child in the family among three siblings. In the physical examination, the patient was oriented to time, place, and person but ill. Vital signs were stable. Cranial nerve examination was normal and symmetric. Right and left sides extensors and flexors limb forces were 5/5 and 3/5, respectively, according to the Medical Research Council (MRC) grading. Deep tendon reflex was increased on the left side. Magnetic Resonance Imaging (MRI) showed a well-defined cystic lesion with a solid mural component and a compression effect on the ipsilateral ventricular system. The lesion had significant peripheral enhancement in the cystic part, and the solid component was located in the right parietal lobe. Tumor lesions such as glioblastoma multiforme, anaplastic astrocytoma, and less likely pleomorphic xanthoastrocytoma were suggested. Surgery was done, and the specimen consisting of several gray fragments measuring 2x1.5x1cm was removed. The pathologist reported compatibility with glioblastoma multiforme, giant cell variant (**Figure 1**). Histopathology showed poorly differentiated and multinucleated giant cells (composed of astrocytes) with bizarre nuclei, abundant eosinophilic cytoplasm, and deposits of reticular fiber in the glioblastoma background.

The patient was readmitted on July 28, 2020, with a headache since the previous month. Headache was more severe at night and was accompanied by nausea and vomiting. The patient had received 30 sessions of radiation therapy. The last session of radiation was nine months earlier. In physical examination, right and left sides flexors and extensors forces were 4/5 and 3/5 respectively on both upper and lower limbs according to MRC grading. Except for the scar of the previous surgery, other findings were unremarkable. The patient underwent surgery again. The removed specimen consisted of several gray pieces measured 5x3x2cm and the pathologist confirmed the recurrence of the tumor (**Figure 2**). After the second surgery, the patient was treated with temozolomide 220mg, and the dosage was increased to 300mg in the last two months. At the last follow-up on January 2021, the patient was in fair condition with no seizure or headache. Written informed consent was obtained for the report.

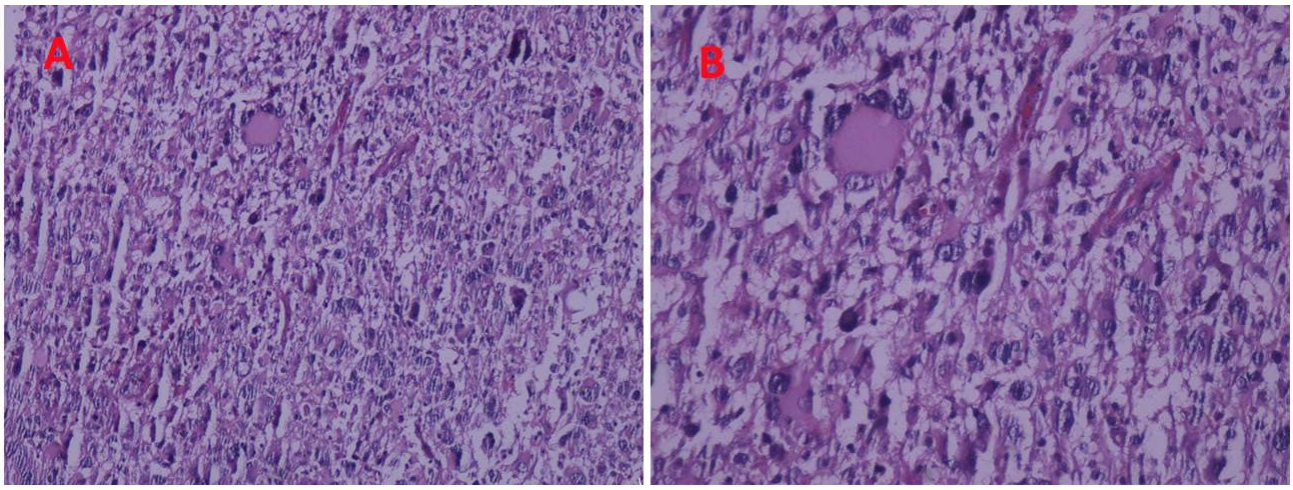


**Figure 1.** Giant cell glioblastoma multiforme. Poorly differentiated and multinucleated giant cells (composed of astrocytes) with bizarre nuclei, abundant eosinophilic cytoplasm, and deposits of reticular fiber in the glioblastoma background. Hematoxylin-Eosin stain, A) X100, B) X200, magnifications.

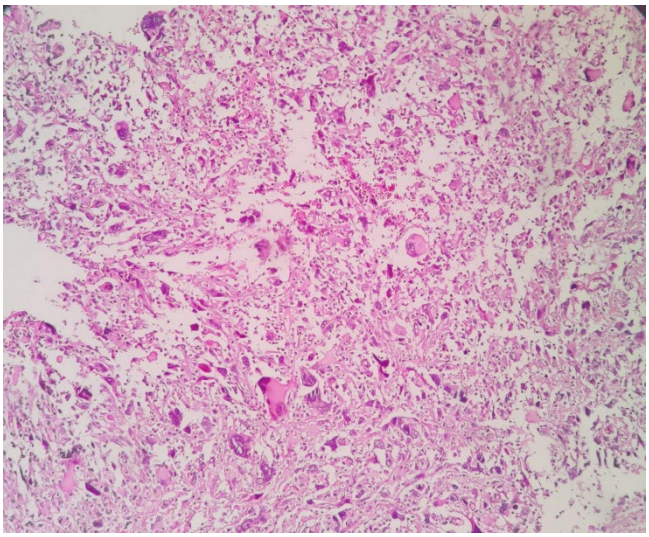

**Figure 2.** Giant cell glioblastoma multiforme. Recurrent tumor, multinucleated giant cells with bizarre nuclei are shown (Hematoxylin-Eosin stain, X100 magnification).

## DISCUSSION:

Glioblastoma is a common malignant glial tumor (15-50%) and is the most common primary fatal nervous tumor (3, 4). According to the WHO, it is considered a grade IV diffuse astrocytic tumor (2). Malignant glial tumors are less common in children than adults and account for 5-10% of brain tumors (5). Giant cell variant is a rare subtype of glioblastoma, accounting for about 0.8% of brain tumors and 5% of glioblastoma tumors (1, 3). Due to the low prevalence of this variant, available information is limited (2). Giant cell glioblastoma is a male predominant tumor in children and adults. The mean age of this variant is 10.4 years in children and 42 years in adults, and there is no histological difference between the adult and children giant cell glioblastoma (2, 3, 6). Most cases of these tumors are sporadic. However, cases have been reported in association with Turcot syndrome, Neurofibromatosis 1, and li- Fraumeni syndrome (1-3, 7, 8). Except for a history of radiation, no risk factor for glioblastoma is known (8). Frequently reported giant cell glioblastoma in the supratentorial subcortical region in the temporal, parietal and frontal lobes. However, rare cases of giant cell glioblastoma in the cerebellum, cerebellopontine angle, lateral ventricles, spinal cord, and even multifocal cases have been reported (1, 3, 5, 6, 9, 10). The duration of clinical symptoms of glioblastoma is short (often less than six months), and there is no much difference in clinical symptoms of the common and giant cell variant (3, 5, 10, 11). The only difference is that the age and the duration of symptoms in giant cell variant are less than other glioblastoma subtypes (1, 12). Although GC-GBM has more cerebral hemispheres involvement, the giant cell glioblastoma cannot be distinguished from the common subtype glioblastoma based on radiology. Differential diagnosis of glioblastoma in radiology imaging consists of metastasis and intracranial hemorrhage (3, 10, 11). On MRI, the giant cell glioblastoma has a heterogeneous appearance with contrast enhancement due to the presence of necrosis, cystic, and solid areas (3, 4). Immunohistochemistry staining is necessary to rule out other differential diagnoses and shows positive staining for GFAP, Vimentin, S100 protein, and alpha -1 antichymotrypsin with increased staining intensity for P53 and Ki-67 and decreased staining intensity for Epidermal Growth Factor Receptor (EGFR) (12, 13). GC-GBM has a better prognosis than the common subtype glioblastoma by a slight increase in survival time. Fibrous stroma around the tumor causes circumferential and well-defined borders of the tumor in histology and radiology views. This feature of GC-GBM allows complete resection of the tumor (3, 11, 14). Good prognostic factors for the GC-GBM include younger patients <40 years and well-defined tumor borders. However, sex is not a prognostic factor (8, 11, 15). Familial patterned and syndrome-associated GC-GBMs have a better prognosis because they have aggressive treatment (12). GC-GBM survival time is about 12 months, while survival time of more than three years, usually uncommon in glioblastoma, is considered long (5, 7, 8). Only 3-5% of cases have a long survival time. Twenty percent of GC-GBM with long survival time are anaplastic astrocytoma and pleomorphic xanthoastrocytoma with misdiagnosis (15, 16). In the microscopic examination, inflammatory cells and giant cell variety are associated with better survival time (10, 12). Toni Rose Jue and colleagues suggested that a long survival time is associated with hypermutated genotypes and is increased by treatment based on the patient's genotype16. GC-GBM has more genetic abnormalities and genetic changes such as TP53 mutations, P53 mutations, deletion of chromosome 10, and microsatellite instabilities (2). It also has higher DNA double-strand breaks than other glioblastoma variants (14, 15). GC-GBM is differentiated from anaplastic astrocytoma by rapidly clinical symptoms, more mitoses, and the pres-

ence of pleomorphic cells (10). Metastatic melanoma can be diagnosed due to the presence of atypical cells. Meanwhile, immunohistochemistry can help with diagnosis (7). Pleomorphic xanthoastrocytoma (PXA) is different that necrosis and abundant mitoses are seen in GC-GBM. Another method is an investigation of gene mutations. PXA and GC-GBM are associated with BRAF and TP53 mutations, respectively (1, 4, 10, 13, 14, 17). Gliosarcoma may arise due to the radiotherapy effect, and GC-GBM tends to occur at younger age and circumferential borders in radiology and histology (2, 18). Supratentorial Primitive Neuroectodermal tumor is especially seen in children (19). The standard protocol for the treatment of GC-GBM is surgical excision and adjuvant chemotherapy, which is a good treatment for long-term survival (8). Extracranial metastasis (ECM) of glioblastoma is rare and is seen in less than 2 % of glioblastomas. Metastasis to the Lung, pleura, regional lymph nodes, bone, and liver is seen. Bony metastasis of GBM are often multiple and associated with metastasis to other organs. The interval time between the diagnosis of the initial tumor and ECM is about 18 months, and the time-to-death is about two months. Therefore, extracranial metastasis of GBM is considered a poor prognostic factor. An important issue is a need for histological examination of tumor metastasis to rule out other differential diagnoses. Immunohistochemistry, especially for GFAP, is necessary for distinguishing the multinucleated glial giant cells from osteoclasts (20).

## CONCLUSION:

We reported a rare brain tumor in an 11-year-old female child presented with rapidly progressive neurologic signs and symptoms and a well-defined brain tumor in MRI. Then the patient underwent surgery. After diagnosing GC-GBM based on histological examination, the patient was treated with radiotherapy. Despite the better prognosis of this variant than other glioblastoma subtypes, the tumor recurred, and the patient underwent reoperation. Based on radiology, the giant cell glioblastoma cannot be distinguished from the common subtype glioblastoma. The pathologists must be aware of this entity, and histologic differential diagnoses are warranted for diagnostic, prognostic, and therapeutic purposes.

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## CONFLICT OF INTERESTS:

The authors declare that there is no conflict of interest.

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