# Variegated colors of pediatric glioblastoma multiforme: what to expect?

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## Abstract

Malignant gliomas account for 35-45% of primary brain tumors; among these glioblastoma multiforme (GBM) is the most common adult brain tumor constituting approximately 85%. Its incidence is quite less in the pediatric population and treatment of these patients is particularly challenging. Exposure to ionizing radiation is the only environmental factor found to have any significant association with GBM. Several genetic alterations associated with GBM in adults have been well documented such as epidermal growth factor receptor amplification, overexpression of mouse double minute 2 homolog also known as E3 ubiquitin-protein ligase, Phosphatase and tensin homolog gene mutation, loss of heterozygosity of chromosome 10p and isocitrate dehydrogenase-1 mutation. However, data on genetic mutations in pediatric GBM is still lacking. Exophytic brain stem gliomas are rare tumors and are usually associated with a poor prognosis. The most effective treatment in achieving long-term survival in such patients, is surgical excision of the tumor and then chemoradiotherapy followed by adjuvant chemotherapy by temozolomide. This schedule is the standard treatment for GBM patients. In view of the rarity of pediatric GBM, we report here a case of pontine GBM in a 5-year-old girl.

## Introduction

Malignant gliomas account for 35-45% of primary brain tumors, out of which 85% are glioblastoma multiforme (GBM), the most common adult brain tumor.[1] It is uncommon before 20 years of age and is rare in the pediatric population. Exposure to ionizing radiation is the only environmental factor found to have any significant association with GBM.[2] We report the case of a 5-year-old girl with a histopathologically proven diagnosis of exophytic pontine GBM presenting with sudden onset of symptoms which, to our knowledge, is rarely reported in literature.

## Case Report

A 5-year-old girl, with normal milestones since birth, was brought to casualty with complaints of sudden onset of vomiting, slurring of speech and difficulty in walking. General physical examination revealed left sided spastic hemiparesis, unequal sluggishly reacting pupils with E2V1M3. She was stabilized and subjected to a contrast-enhanced magnetic resonance imaging (CEMRI) whole brain, which revealed a neoplastic process involving the left pons and the left middle cerebellar peduncle including the cerebellopontine angle (Figure 1). The exophytic component of the tumor was seen extending into the mid brain and medulla causing mass effect.

She was taken up for emergency surgery and left sided retrosigmoid sub-occipital craniotomy with excision of the pontine tumor was done under general anesthesia.

Histopathological examination revealed a cellular tumor with variegated appearance composed of neoplastic astrocytes arranged in sheets with a fibrillary background in some places. The tumor cells show marked pleomorphism with scattered giant bizarre uninucleate and multinucleate tumor cells. Most of the tumor cells had round to irregular pleomorphic hyperchromatic nuclei with prominent nucleoli in some cells. Frequent mitoses and foci showing microvascular proliferation were also present, suggestive of GBM, World Health Organization (WHO) grade IV. In view of young age and the rarity of these tumors in children, immune histochemical examination was performed to confirm the histopathological diagnosis. Immunohistochemistry (IHC) was done using standard protocols as per the manufacturer's instructions. Ready-to-use primary antibodies were procured from Biogenex Laboratories Inc, USA. The polymer detection kit was obtained from Leica Microsystems, UK. Appropriate positive and negative controls were used and were found to be satisfactory. The tumor cells were diffusely positive for glial fibrillary acidic protein and vimentin, focally positive for epithelial membrane antigen and cytokeratin, and negative for CD99 and spinal muscular atrophy. The Ki67 proliferative index was 60% prompting towards a highly aggressive tumor. IHC findings confirmed the diagnosis of GBM (Figure 3). The patient was planned for adjuvant treatment in the form of chemoradiation with concurrent temozolomide, however, the patient did not come for further treatment and hence, post-operation imaging could not be done.

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## Discussion

GBM is a grade IV astrocytoma, which is one of the most aggressive brain tumors. It accounts for approximately 17% of all adult intracranial neoplasms.[3] However it is rare in the pediatric population.[4] The incidence of GBM in pediatric patients is quite low and values range 4.5-8.8% as reported in several retrospective analyses.[5,6]

Infratentorial high-grade gliomas constitute only 3-9% of the pediatric high-grade gliomas. The peak incidence for this tumor is around 6 to 9 years of age. The term glioma encompasses various tumor types such as ganglioglioma, pilocytic astrocytoma, fibrillary astrocytoma, anaplastic astrocytoma and glioblastoma multiforme.[7] Most infratentorial high-grade gliomas tend to be diffuse intrinsic pontine gliomas which account for 80% of brainstem gliomas, however, in our patient it was an exophytic pontine glioma which is rare. We

are reporting this case because of the rarity of pediatric GBM arising *de novo* at an uncommon pontine site with acute presentation with sudden onset of vomiting, slurring of speech and difficulty in walking.

GBM in adults is found to occur most commonly in the subcortical white matter of the cerebral hemispheres. Majority of these occur in the temporal lobe followed by the parietal, frontal and occipital lobes.[8]

Glioblastomas in the brainstem, cerebellum and spinal cord are rare and these sites are usually seen in pediatric patients. Exophytic brain stem gliomas arise from the sub ependymal glial tissues and expand outside the pons. However, the area of extension is into the fourth ventricle unlike our patient where the area of extension was mainly into the middle cerebellar peduncle

GBM is usually sporadic but may also be associated with hereditary syndromes like Li-Fraumeni syndrome and Turcot syndrome.[9] Primary GBM arises in the absence of any precursor lesion and is more common in adults. Secondary GBM can arise from astrocytoma and is seen in pediatric population, but in our case it was primary GBM arising de novo in the pediatric age group.

Exposure to ionizing radiation is the only environmental factor found to have any significant association with GBM.[10] Children who have received prior radiation as part treatment of low-grade gliomas are at an increased risk of developing glioblastoma. However in our patient, there was no history of exposure to ionizing radiation in utero or as part of treatment of a low-grade glioma.

Progressive neurological deficit is usually the presenting complaint in adults unlike pediatric age group where the clinical pres-

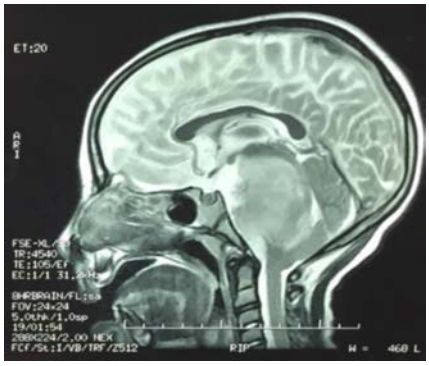

**Figure 1. Pre-operative contrast-enhanced magnetic resonance imaging showing a neoplastic process involving the left pons, the left middle cerebellar peduncle including the cerebellopontine angle with exophytic component extending into the mid brain and medulla.**

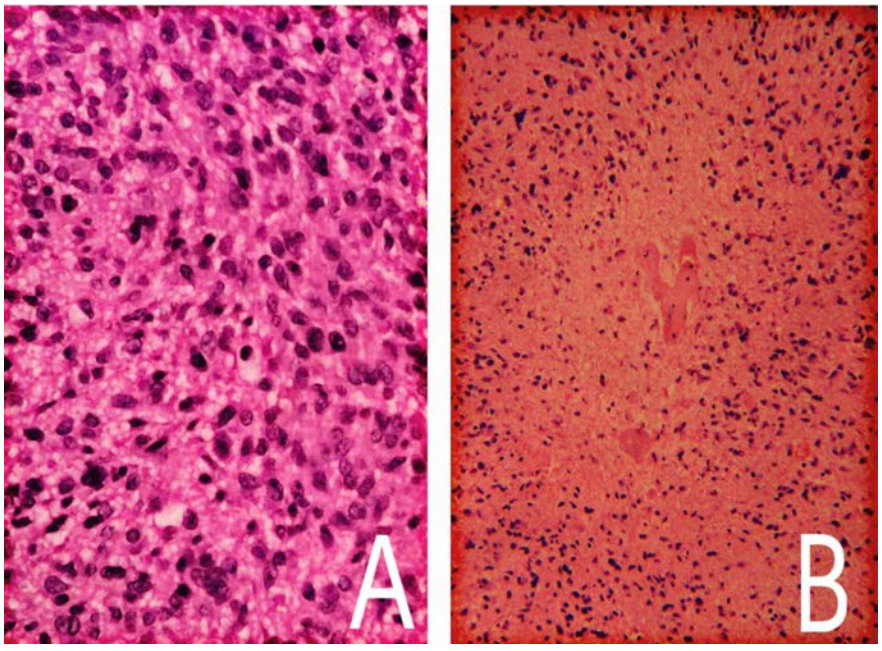


**Figure 2. A) Photomicrograph showing tumor cells (400×); B) photomicrograph showing bizarre multinucleated giant cells, central area of necrosis with focal hemorrhages with peripheral palisading of tumor cells (100×).**

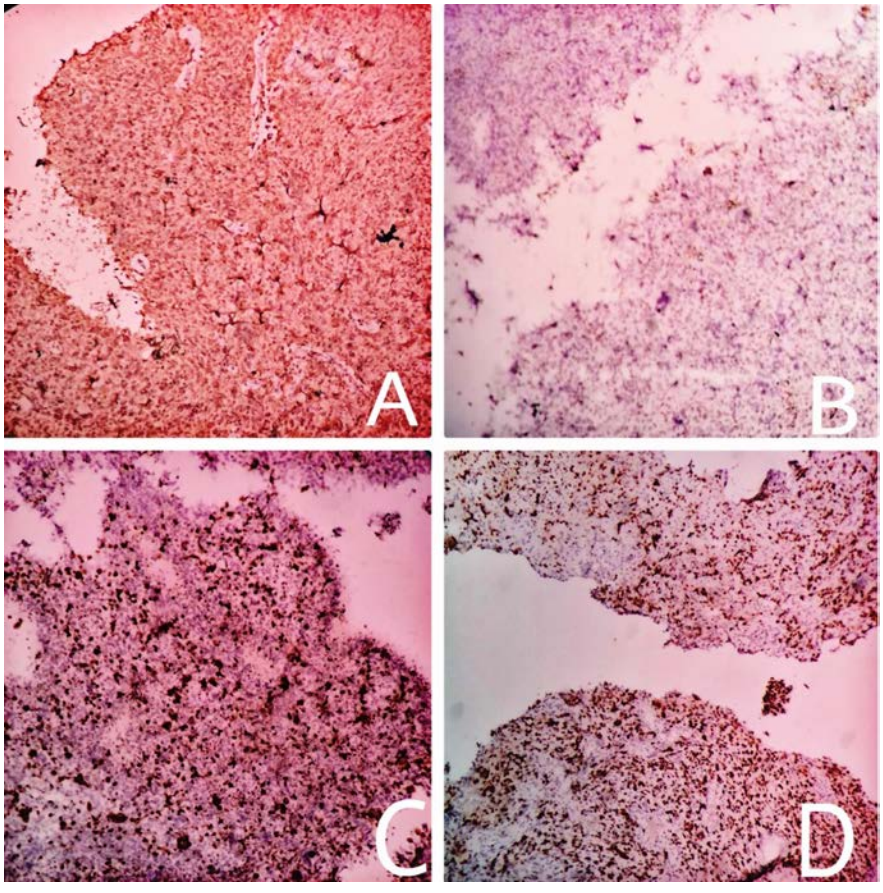


**Figure 3. A) Photomicrograph showing immunoexpression of glial fibrillary acidic protein by tumor cells; B) photomicrograph showing tumor cells negative for CD99; C) photomicrograph of Ki-67 immunostaining showing proliferative index of 60%; D) photomicrograph showing tumor cells positive for p53.**

entation is dependent on the site of the tumor. The clinical presentation can vary from generalized signs and symptoms like failure to thrive, developmental delay, excessive irritability and crying to more specific and localizing signs and symptoms like ataxia, motor and/or sensory deficit. A proportion of children can present with features suggestive of increased intracranial pressure. Our patient presented with signs of increased intracranial pressure along with motor deficit and ataxia, which could be attributed to posterior fossa involvement. Surprisingly, our patient did not present with cranial nerve involvement as would be expected in a case of exophytic brain stem glioma. On magnetic resonance imaging (MRI) glioblastoma appear as large tumors with thick, irregular-enhancing margins and a central necrotic core, which may also have a hemorrhagic component, which was in accordance with the MRI findings in our patient which showed a large grey matter isointense heterogeneously enhancing mass in the region of the left pons, left middle cerebellar peduncle and left midbrain with exophytic component involving the left cerebellopontine angle with few hemorrhagic areas and areas of necrosis (Figure 2).

According to WHO definition, a grade IV glioma is a diffusely infiltrative astrocytic tumor with cytological atypia, anaplasia, mitotic activity, microvascular proliferation and/or necrosis, which was in accordance with the histopathological findings in our patient.[1]

Three tumor markers for gliomas have been proposed and these can be used to classify patients into subtypes. These markers are: mutation in telomerase reverse transcriptase (*TERT*) promoter, mutation in IDH and co-deletion of 1p/19q. Patients with triple negative disease (IDH, *TERT*-, 1p19q intact) usually have a poorer overall prognosis.[12]

There are several studies that have been done on genetic alterations in glioblastoma in adults, however, the data on genetic alterations in pediatric GBM is quite scanty and appear to be distinct from those in adult GBMs.

Primary glioblastomas tend to have amplification of epidermal growth factor receptor (*EGFR*) and overexpression of mouse double minute 2 homolog, mutation of phosphatase and tensin homology deleted on chromosome 10 (*PTEN*) and/or loss of heterozygosity of chromosome 10p. IDH1 mutation helps in differentiating between primary and secondary glioblastomas.[8] Unlike primary tumors, secondary glioblastomas tend to be IDH-1 mutant (positive), and demonstrate p53 mutations, amplification of platelet derived growth factor A, loss of heterozygosity of chromosomes 10q and 17p, loss of 19q and increased telomerase activity and human TERT (*hTERT*) expression.

Alterations of *PTEN* and amplification of *EGFR* are uncommon in pediatric GBM.[8] A large majority of cases showed p53 protein expression along with loss of p16 and p27 expression. The tumor specimen in our patient was found to be positive for p53 expression. Some glioblastomas may have an oligodendroglial component with a variable frequency of 1p and 19q deletion. In a recent study 1p deletion was found in 6.2% and 19q deletion was found in 5.3% of glioblastomas, however these did not correlate with overall survival of the patients.[13]

*PIK3CA* mutation is also seen in about 21% of pediatric glioblastomas, suggesting that this pathway might be a potential therapeutic target in the management of pediatric GBM.[1] Further testing for genetic markers could not be done in our patient, as the patient was lost to follow-up after surgery. In view of the variation in the genetic alterations in pediatric GBM as compared to adult GBM, the validity of application of therapeutic strategies being used in adults, to pediatric GBMs is uncertain.

GBM has a poor prognosis with a median survival of 1 year. The good prognostic factors associated with GBM include young age, complete resection and good performance status.[15] The median overall survival is 43 months with a progression free survival of 12 months in pediatric patients.[16] Surgical resection of the tumor along with chemoradiotherapy followed by chemotherapy with temozolomide has been found to be the most effective regimen in the management of such patients and has shown an improvement in survival in GBM patients.[17] Though temozolomide improves survival in adult patients, it has not been found to improve survival in pediatric brain tumors.[18] Several studies have confirmed the lack of significant impact of radiotherapy with concomitant temozolomide on outcome in pediatric patients. Therefore the role of temozolomide in pediatric tumors remains uncertain, at best.

## Conclusions

GBM is an aggressive disease with poor prognosis. In spite of multimodality treatment survival is short. While the genetic alterations occurring in glioblastoma in adults are well documented, the data in pediatric tumors is lacking. Therefore, there is a need for further investigation to determine the molecular alterations, which may give rise to GBM in children so that new therapeutic modalities can be tailored specifically to needs of the pediatric population.

## References

1. Woo SY. The brain and spinal cord. In: Cox JD, Ang K, eds. Radiation oncology. Rationale, technique, results. Philadelphia, PA: Mosby Elsevier; 2010. pp 835-71.
2. Sathornsumetee S, Rich JN. New treatment strategies for malignant gliomas. Expert Rev Anticancer Ther 2006;6: 1087-104.
3. Katz DS, Poe LB, Winfield JA, Corona RJ Jr. A rare case of cerebellar glioblastoma multiforme in childhood: MR imaging. Clin Imaging 1995;19:162-4.
4. Kleihues P, Burger PC, Aldape KD, et al. Glioblastoma. In: Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, eds. WHO Classification of Tumours of the Central Nervous System. Lyon, France: IARC Press; 2007. pp 33-49.
5. Sánchez-Herrera F, Castro-Sierra E, Gordillo-Domínguez LF, et al. Glioblastoma multiforme in children: experience at Hospital Infantil de Mexico Federico Gomez. Childs Nerv Syst 2009;25:551-7.
6. Dohrmann GJ, Farwell JR, Flannery JT. Glioblastoma multiforme in children. J Neurosurg1976;44:442-8.
7. Rasalingam K, Abdullah JM, Idris Z, et al. A rare case of paediatric pontine glioblastoma presenting as a cerebellopontine angle otogenic abscess. Malays J Med Sci 2008;15:44-8.
8. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. Am J Pathol 2007;170:1445-53.
9. Krex D, Klink B, Hartmann C, et al. Long-term survival with glioblastoma multiforme. Brain 2007;130:2596-606.
10. Adamson C, Kanu OO, Mehta AI, et al. Glioblastoma multiforme: a review of where we have been and where we are going. Expert Opin Investig Drugs 2009;18:1061-83.
11. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007;114:97-109.
12. Eckel-Passow JE, Lachance DH, Molinaro MA, et al. Chromosome 1p and 19q deletions in glioblastoma multiforme. Appl Immunohistochem Mol Morphol 2009;17: 512-76.
13. Kaneshiro D, Kobyashi T, Chao ST, et al .Different treatment strategies and predictive factors. Strahlenther Onkol 2007;183:695-702.
14. Gallia GL, Rand V, Siu IM, et al. PIK3CA gene mutations in pediatric and adult glioblastoma multiforme. Mol Cancer Res 2006;4: 709-14.

15. Filippini G, Falcone C, Boiardi A, et al. Prognostic factors for survival in 676 consecutive patients with newly diagnosed primary glioblastoma. Neuro Oncol 2008;10:79-87.
16. Song KS, Phi JH, Cho BK, et al. Long-term outcomes in children with glioblastoma. J Neurosurg Pediatr 2012;6:145-9.
17. Piroth MD, Gagel B, Pinkawa M, et al. Postoperative radiotherapy of glioblastoma multiforme: analysis and critical assessment of different treatment strategies and predictive factors. Strahlenther Onkol 2007;183:695-702.
18. Cohen KJ, Heidman R, Zhou T, et al. Should temozolomide be the standard of care for children with newly diagnosed high grade gliomas? Results of the Children's Oncology Group ACNS0126 study. Neuro Oncol 2007:9.