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(CASE REPORT)

Recurrence of glioblastoma multiforme in a childhood: A case report

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Abstract

GBM is a highly aggressive malignant tumor that rarely happens in children. Pediatric GBM is the primary cause of death in children with brain neoplasms. Treatment of GBM is a difficult and challenging condition, especially in pediatric GBM. Surgical tumor resection combined with chemoradiotherapy suggests as standard therapeutic approaches for GBM. However, the recurrence of GBM is an inevitable event and can occur in more than 90% of patients. We present an unusual case of an 11-years-old girl with recurrence of GBM. She complained of progressive headache and left hemiparesis as an initial manifestation. She was diagnosed with GBM three years before. Near-total surgical resection followed with chemotherapy, and radiotherapy was done after the diagnosis. Head imaging showed a smaller lesion, and her symptoms were improved significantly. Two years after, she was admitted to the hospital with worsening symptoms. Imaging evaluation showed the enlargement of tumor lesions. Recurrence of GBM is a great challenge to manage, and there are no well-defined management protocols. Several studies suggest that treatment options may follow the adult patients' approach, but pediatric GBM has significantly different characteristics than adults.

Keywords: Glioblastoma Multiforme; Recurrence; Pediatric; Childhood

1. Introduction

Glioblastoma multiforme (GBM) is a highly aggressive malignant primary brain tumor which manifests at any age, mostly in the older age group, with a male predominance. GBM in pediatrics is an unusual case and happens around 3% of all childhood brain tumors [1–3]. GBM is the primary cause of death with high mortality in children with brain neoplasms [4]. Children with GBM have a poor outcome, and low survival rates range from 5% to 15% in 5 years [2,5–7].

Treatment of GBM in childhood is a difficult and challenging condition [1,5]. Recent data support aggressive surgical resection combined with chemotherapy and radiotherapy, but GBM can recur and are ultimately incurable [1,8]. Recurrence is an unavoidable event in the natural history of GBM and poses a significant challenge to manage [9]. Here, we report a rare case of an 11-year-old girl with recurrence of GBM and undergo the repeated operative procedure. Considering developments and advances in the study of GBM, aspects of clinical features, diagnosis, treatment, and prognosis of pediatric GBM will discuss.

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2. Case Report

An 11-year-old girl was admitted to the hospital because of progressive headache and left hemiparesis. She had no history of head trauma or familial disease. On the initial admission examination, her mental status was compos mentis with GCS 15 and normal vital signs. Neurological examination showed pupils equally reactive bilaterally with no papilledema. There was a decrease in motor strength of her left extremity with motor power 3/5.

There was a history of progressive hemiparesis from 3 years before, and she had been diagnosed with a brain tumor. Repeated surgical resection was done as early treatment for a brain tumor. She underwent the first surgical resection procedure three years ago to reduce the near total of the lesion. Histopathology examination of the tumor tissue confirmed the diagnosis of Glioblastoma Multiforme (GBM). The symptoms were improved significantly after resection. Less than one year after following the diagnosis, she complained of neurological worsening with heavier progressive hemiparesis in her left extremity. Head magnetic resonance imaging (MRI) results showed regrowth tumor and an increase of the lesion size. This recurrence was treated with the second near-total surgical resection, followed by chemotherapy and radiotherapy. Head imaging showed a smaller lesion, and her symptoms were improved significantly. We did head MRI routinely to evaluate tumor progression. Figure 1 and Figure 2 showed head MRI evaluation three months and seven months after the second tumor resection, respectively.

The patient complained of neurological worsening almost two years after the second resection procedure. We performed head MRI evaluation and showed regrowth tumor signed as an irregularly shaped expansive intra-axial heterogeneous lesion with bleeding component and contrast-enhanced on the right of cerebral hemisphere measuring approximately 6.7 x 8.8 x 7.2 cm. This huge mass was associated with vasogenic edema, obstructive hydrocephalus, and a 13 mm midline shift to the left hemisphere (see Figure 3). MR Spectroscopy (MRS) showed intralesional persisting raised choline/creatinine ratio and choline/NAA ratio. MR Tractography showed a decrease in the right corticospinal tract fiber. Based on these results and her medical history, neurological examination, histopathology, and head imaging, the patient was diagnosed with recurrence GBM.

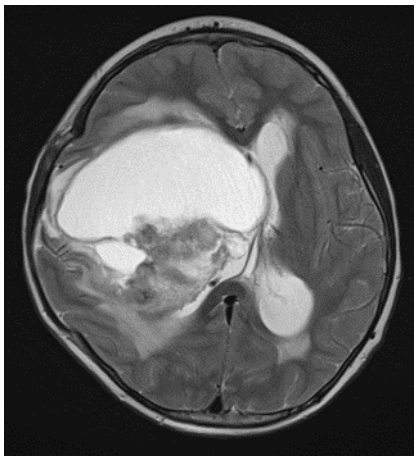

Figure 1 Brain contrast magnetic resonance imaging 3 months after the second surgery and chemoradiotherapy showing irregularly shaped intra-axial mass, associated with vasogenic edema, obstructive hydrocephalus, and midline shift (size approximately 9.37 x 8.35 x 6.5 cm).

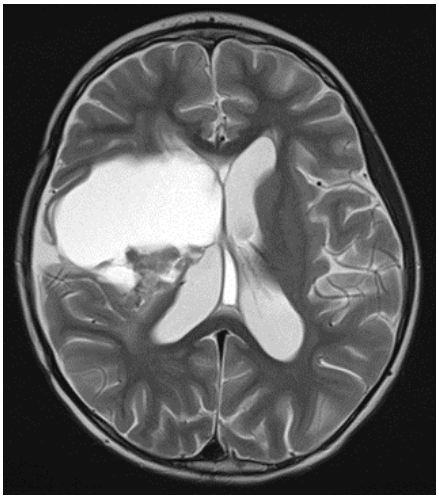

Figure 2 Brain contrast magnetic resonance imaging 7 months after the second surgery and chemoradiotherapy showing irregularly shaped intra-axial mass, smaller lesion compared with previous imaging (size approximately 6.36 x 6.89 x 6.49 cm)

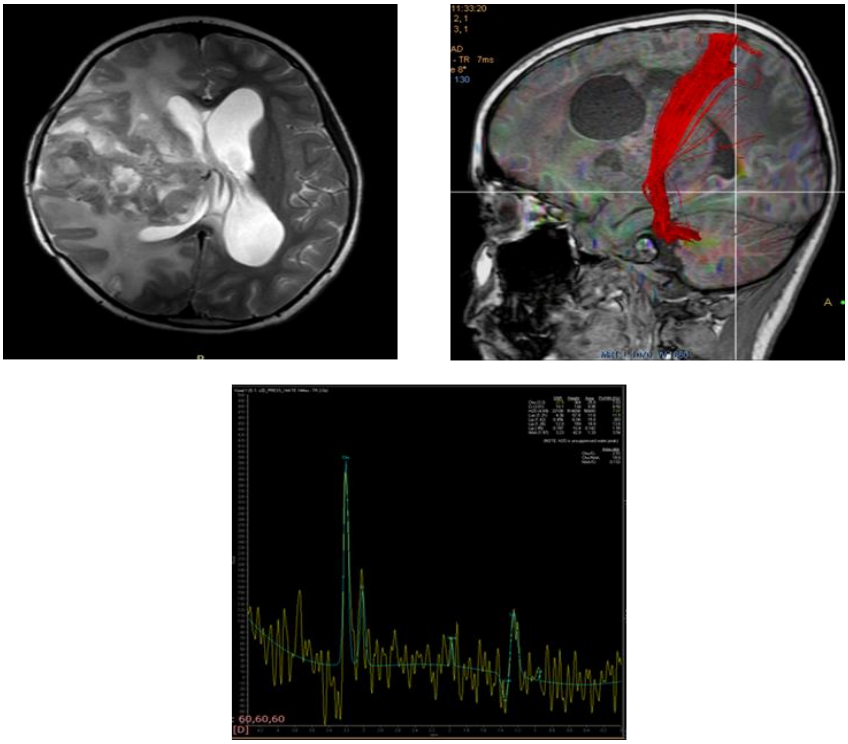

Figure 3 Brain contrast magnetic resonance imaging almost 2 years after the second surgery showing irregularly shaped expansive right intra-axial heterogeneous lesion with bleeding component (size approximately 6.7 x 8.8 x 7.2 cm) and associated with vasogenic edema, obstructive hydrocephalus, and midline shift. MR Spectroscopy showed intra and peri-lesional persisting raised choline/creatinine ratio and choline/NAA ratio. MR Tractography showed a decrease in the right corticospinal tract fiber.

3. Discussion

Glioblastoma multiforme (GBM) is an unusual pediatric case, with a prevalence of around 6.5% of all intracranial neoplastic [2,5]. The mean age of GBM in childhood varied between 8.8-12.7 years [10]. There is a male predominance with the ratio between males and females was 1.5:1, or in other reports was 3:2 [5,10]. They are most frequently located in the cerebral hemispheres, cerebellum, and the thalamus or hypothalamus, although they may occur anywhere of the

central nervous system anatomical sites [1,2,5]. The frontal lobe is the most frequent area consisting of 25-35% of childhood with GBM. GBM in the central area has higher mortality as compared to the hemispheric location [2,7,10].

There are two subtypes of GBM depend on the clinical and morphologic basis. The first one is primary GBM, defined by short patient history and absence of a precursor or pre-existing less malignant lesion. Primary GBM usually occurs in an adult population. The second one is that secondary GBM develops more slowly from astrocytoma within several years. The majority of patients had primary GBM [3,10,11].

Published studies showed that pediatric GBM has significant differences compared with adults. Children with GBM has a different and more pleasing natural history, different cell mutations, and different respond to the same chemotherapeutic treatments as adult GBM [12]. Pediatric GBM has better survival outcomes than adults. Genomic profiles between pediatric and adult GBM are different, such as phosphate and tensin homolog (PTEN) deletions, and epidermal growth factor receptor (EGFR) amplification is common in adults GBM, but rarely in pediatric. Loss of PTEN expression correlate with poorer outcomes in pediatric GBM, this condition explains survival disparity between adults and pediatric GBM. Alpha-type platelet-derived growth factor receptor (PDGFRA) is increase and overexpressed in pediatric GBM compared with adults. Several mutations are only seen in pediatric GBM, including mutations in ACVR1 genes, histone H3.3, and other chromatin remodeling genes. Pediatric GBM may have preexisting conditions, such as neurofibromatosis type I, Turcot syndrome, and Li-Fraumeni syndrome, causing tumor growth through different pathways compared with adults [12]. Overexpression of p53 protein was reported by approximately 53.7%-63% in pediatric glioblastoma. MGMT protein expression may occur in 12%-70% of the high-grade gliomas in pediatric [6,7]. Younger children are associated with a lesser number of mutations [7].

In this report, hemiparesis and cephalgia are neurologic manifestations as the leading cause of presentation to the hospital and diagnosing brain lesions. Children with GBM can present various signs and symptoms that mainly depend on their age and anatomical localization. Progressivity in neurological impairment is typically rapid and ranges from days to months. Clinical manifestations include hemiparesis, headache, nausea, vomiting, visual problems, ataxia, vertigo, gait disturbance, and the sign of raised intracranial pressure. If tumors location near the cerebral cortex, a seizure may happen initially [1,3,5].

Head imaging is one of the supporting ways for diagnosing GBM, especially using MRI. On MRI with contrast, GBM showed a huge mass enhanced contrast, while low-grade gliomas frequently slightly or not enhance with contrast. MR Spectroscopy (MRS) is an advanced non-invasive technique to evaluate the metabolic profile of the brain. In most CNS malignancies, MRS showed increased choline levels and reduced NAA levels [1,2,5]. In this report, there was an irregularly shaped expansive lesion with contrast enhancement on the cerebral hemisphere, with vasogenic edema, obstructive hydrocephalus, and cerebral herniation. These findings are consistent with the literature about imaging on GBM. However, only with histopathology examination can confirm the diagnosis [1].

Treatment of GBM is a difficult, highly resistant, and challenging condition, mainly in children [1,2,5]. Currently, clinicians focus on surgical tumor resection with adjuvant concomitant chemoradiotherapy as standard therapeutic approaches for GBM. This treatment approach is compatible with children older than 3-5 years of age, consistent with the avoidance of radiation-related to secondary potential long-term neurological deficits [1,2,7,11,12]. Usually, complete resection is hard to achieve because of the tumor's infiltrative margin, fragile overlying vasculature, and intricacy of the surgery. After resection, GBM can recur and are ultimately incurable [2,8,11]. This choice of treatment focuses on improving survival rates but does not change the course of the disease. The average survival for GBM is one year, and after combined with adjuvant concomitant chemoradiation, improve survival for only two months [2,11]. Repeat surgery procedure for GBM can be indicated individually and was associated with a higher survival time [10]. As happened in our patient, she had undergone several surgical procedures combined with chemotherapy and radiotherapy, but tumor lesions regrowth and became more prominent than the initial lesion.

Recurrence in GBM is an inevitable event and can occur in more than 90% of patients [3,9]. Recurrence can develop in the local area or with extension to other areas of the brain. The median interval from diagnosis to the recurrence of the tumor was around 12 months. Diagnosis of recurrence GBM was a difficult and definitive diagnosis only with histopathology examinations [3]. The main differential diagnosis includes radiation necrosis, which can occur in the same period with the recurrence of GBM. However, recent advances in imaging modality can help to differentiate between the two [9].

The treatment of recurrence GBM was challenging, associated with significant toxicities, and balanced between local control and treatment-related morbidities and mortalities. Some literature treats the tumor's recurrence in a supportive manner, high dose steroids and morphine [3,9]. Surgery in recurrent GBM focuses on reducing the tumor, relieving the

symptoms, and evaluating the morphological structure. Reoperation can increase survival rates when performed in patients with a KPS of at least 60 [6,9]. Re-irradiation can be considered in patients with small-volume recurrence, distance from the primary area of irradiation, the longer time interval between recurrence and first irradiation, and if surgery is not possible to do. Although re-irradiation can do after six months, the ideal timing is patient recurring after two years. Additional toxicity in re-irradiation must be kept in mind when we planned for re-irradiation. Chemotherapeutic drugs are also used in recurrent GBM to improve disease control [9]. Several studies suggest that treatment options may follow the adult patients' approach, but pediatric GBM has significantly different characteristics than adults. In our case, recurrence occurs less than one year after the patient did the first tumor resection, and the second resection procedure was done to remove near total of the mass, followed by chemoradiotherapy. We routinely evaluate tumor progression with brain MRI. There was a decrease in tumor size several months after the second tumor resection combined with chemoradiotherapy. However, more than one year after the second resection, the tumor enlarges again, and clinical manifestation appeared.

Current data about treatment effectivity in GBM is still contradictory. Several studies conclude that temozolomide in pediatric GBM was performed with disappointing results and need further studies. Studies have shown that temozolomide can increase only low survival rates and not so effective among pediatrics with GBM. Pediatric GBM frequently does not respond to the same chemotherapy agent as adults GBM, most likely caused by their contrasting genomic characteristics. Surgery, chemotherapy, and radiotherapy were ineffective in reaching long-term survival in GBM. Moreover, some studies conclude that chemotherapy and radiotherapy are associated with increased morbidity [1,4,5,11,12].

Prognostic pediatric GBM was very poor [13]. Median overall survival around 14-55 months, and 2-year overall survival from 15-52% [12]. There are some studies about prognostic factors related to GBM. The most decisive prognostic factors are younger age, supratentorial location, the extent of surgical resection of the tumor, and good PS (>60). Other factors, such as midline shift and level of hemoglobin, are also suggested [9,11,12]. Pediatric GBM with deep tumor and the infratentorial location correlates with worse overall survival and poor prognosis [12]. The better outcome is also related to the underlying biology of the tumor. Children with GBM have different biological characteristics compared with adults [8]. Higher survival was found in pediatric GBM with no TP53 mutations compared with pediatric GBM with TP53 mutations, sequentially 42% versus 28% in 5-year survival. They posited these conditions related to increased resistance to the cytotoxic effect of chemoradiotherapy [12].

4. Conclusion

GBM is a rare brain neoplasm with poor outcomes in children. A combination of aggressive treatment with complete tumor resection and adjuvant concomitant chemoradiation is the best therapeutic approach and significant prognostic factor. Despite that, GBM can recur and are ultimately incurable. Recurrence of GBM is a great challenge to manage, and there are no well-defined management protocols. Several studies suggest that treatment options may follow the adult patients' approach, but pediatric GBM has significantly different characteristics than adults. Further research and investigation are necessary to provide protocol guidelines about the management of recurrence pediatric GBM and increase overall patient survival.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors have no conflicts of interest to disclose.

Statement of informed consent

Written informed consent was obtained from the parents of patient in thic case report.

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