Infiltrative multifocal glioblastoma progression in a twelve-year-old boy after COVID-19 infection: a case report

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ABSTRACT

**Background:** Glioblastoma is one of the most malignant types of primary central nervous system tumors with a high recurrence rate and dismal prognosis. Multifocal glioblastoma has been shown to have a poorer prognosis than solitary glioblastoma. Cancer patients are at risk of contracting COVID-19. It is hypothesized that COVID-19 may induce glioma tumorigenesis via angiotensin enzyme 2 receptor. We reported a rare pediatric multifocal glioblastoma in a twelve-year-old boy complicated with COVID-19.

**Case Presentation:** The patient was a twelve-year-old boy with a new-onset unprovoked seizure and headache. Magnetic resonance imaging (MRI) showed a heterogeneous solid cystic mass in the left temporal region (2.1x2.1x2.8 cm) with an increased choline/creatinine ratio and choline/n-acetyl acetate aspartate (NAA) ratio suggestive for high-grade glioma. The patient was contracting COVID-19 shortly after the diagnosis of glioblastoma. Two weeks later, patients came with significant neurological deterioration, hemiparesis, headache, and vomiting. MRI showed an infiltrative mass in the temporal and parietal region (5.05x8.03x8.3 cm) with intratumoral hemorrhage, also causing midline shift deviation (11.9 mm). The patient underwent trepanation and total safe resection of the tumor. Histopathological findings showed neoplastic cells with abundant mitotic figures, necrotic foci and pseudopalisading necrosis. These findings confirmed the diagnosis of multifocal glioblastoma.

**Conclusion:** Glioblastoma is a rare disease in the pediatric population with a poor prognosis due to its infiltrative nature and high recurrence rate. The patient had an acute deterioration of the neurological condition and rapid growth of the tumor after he contracted COVID-19, which may or may not be incidental. Further observation of similar cases will be required to determine the association between glioblastoma and COVID-19.

**Keywords:** Glioblastoma, Pediatric, COVID-19.

**Cite This Article:** Saputra, A., Bajamal, Z., Notopuro, F., Puspitasari, L.D. 2022. Infiltrative multifocal glioblastoma progression in a twelve-year-old boy after COVID-19 infection: a case report. *Intisari Sains Medis* 13(2): 475-479. DOI: 10.15562/ism.v13i2.1337

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INTRODUCTION

Glioblastoma or glioblastoma multiforme (GBM) is the most common primary central nervous system (CNS) tumor in adults, with high recurrence and a dismal 5 years survival rate of <5\%.\(^1\) Although CNS tumors are the second most common neoplasm of childhood after leukemia, GBMs are rare in children and account for only 3% of CNS tumors in the pediatric population.\(^1\),\(^2\) Standard treatments for glioblastoma are surgical removal of the tumor and adjuvant treatments using chemotherapy and radiotherapy. Despite modern technological development and various treatment modalities against GBM, it is still a lethal disease in children with 5 years survival rate of <20\%.\(^3\),\(^4\) COVID-19 outbreak, which threatens the global healthcare system, also complicates treatment for cancer patients. Cancer patients need to go to the hospital frequently. Cancer patients risk contracting severe COVID-19 because of their weakened immune system.\(^5\),\(^6\) COVID-19 is also hypothesized to induce glioma tumorigenesis via angiotensin-converting enzyme 2 receptor molecules overexpressed in glioma cells.\(^7\)

This case report aims to show a rare case of pediatric glioblastoma of a 12-years-old boy complicated with COVID-19. It turned out that COVID-19 influenced the progression of glioblastoma disease in this patient.

CASE REPORT

A previously healthy 12-year-old boy with adequate neuro-psychomotor development presented at the emergency department with a new-onset generalized tonic-clonic seizure for 5 minutes. The seizure stopped spontaneously. After the patient regained consciousness, he complained of a headache, but no neurological deficit was found from a physical examination. The patient was referred to the radiology department for an elective MRI with contrast examination. The MRI showed a lobulated heterogeneous solid cystic mass, measuring 2.1 x 2.1 x 2.8 centimeters in the cortical-subcortical of the left...
temporal region (Figure 1). Post-contrast administration showed heterogeneous contrast enhancement. Dynamic Susceptibility Contrast-Enhanced/ DSC-MR Perfusion showed increased r-CBV/relative-Cerebral Blood Volume (Figure 2). MR spectroscopy showed an increased in choline/ creatinine ratio & choline/ NAA ratio. These findings are strongly suggestive of high-grade glioma. There was no midline shift at that moment.

The patient was referred to a neurosurgeon for elective surgery. The patient was admitted to the hospital and had laboratory examination and reverse-transcriptase polymerase chain reaction (RT-PCR) Sars-CoV-2 for screening before surgery. His RT-PCR result was positive. The surgery was postponed and the patient was treated for his COVID-19. The patient's symptoms were considered mild. No significant respiratory distress and pneumonia were found in the examination. Ten days later, the patient's RT-PCR test was negative and he was discharged from the hospital.

Two weeks later, the patient came to the emergency room with right extremity hemiparesis, headache, and profuse vomiting. One week before, the patient complained of headache and progressive weakness of his upper and lower right limb. He was able to lift his right limb against gravity but fell without any resistance, which concludes his right limb motoric power grade is 3. We also found increased deep tendon reflex in his upper and lower right limb. His left extremities were able to move normally. The patient was admitted to the hospital to get repeated MRI with contrast and surgery to resect the tumor.

MRI with contrast examination was repeated. MRI showed a heterogenous infiltrative mass in the left temporoparietal lobe, necrosis and hemorrhage area intratumoral (+), current size 5.05 x 8.03 x 8.3 cm, with T2-peritumoral hyperintensity, compressing left lateral ventricle & third ventricle, also causing deviation of midline structure to the right 1.2 cm (Figure 3). Post-contrast administration showed heterogeneous contrast enhancement. MR perfusion showed increased r-CBV. MR spectroscopy showed increased choline/creatinine ratio, Choline/ NAA ratio & lipid-lactate. There was a midline shift measured for 11.9 mm. Compared to the previous MRI four weeks ago, there is rapid progression and enlargement of the mass (approximately doubled in mass size), causing increased intracranial pressure significantly, with a deviation of midline structure (Figure 3). Laboratory examinations at admission were unremarkable.

The patient underwent trepanation and total safe resection of the tumor. Skull was opened from parietal to temporal to expose the dura mater. The dura mater was found bulging. The tumor in the parietal area was resected totally near the premotor area. The rest of the tumor in the temporal area was resected totally. Bleeding was stopped, dura mater was repaired and the skull was closed. Histopathological findings of the tumor showed neoplastic cells with hyperchromatic and pleomorphic nuclei, narrow cytoplasm, and abundant...
mitotic figures (Figure 4). Necrotic foci and pseudopalisading necrosis were also observed. These findings confirmed the diagnosis of multifocal glioblastoma (WHO grade IV).

The patient was observed in the high care unit, and a CT scan was performed one day after surgery. CT scan showed pneumocephalus and defect at the temporal lobe 3.4 x 3.2 x 3.7 cm, with minimal subdural fluid collection (Figure 5). After the surgery, he could lift his right limb against gravity but fell without resistance, which concluded his right limb motoric power grade is still 3. The patient’s other symptoms, such as headache and vomiting, improved. The patient was discharged after one week and referred to adjuvant treatment of radiotherapy and chemotherapy. We didn't get any further information about his condition. The patient died two months after the surgery, shortly after the start of radiotherapy treatment.

**DISCUSSION**

This case presented a 12 years old boy with a rare case of GBM in children. GBM in children is relatively rare when compared with its adult counterpart. These patients’ first clinical symptoms are tonic-clonic seizure and headache. Seizures are often observed when the tumor is close to the cerebral cortex. Some studies have noted a relatively higher incidence of seizures in pediatric GBM, unlike in adults. Other common clinical manifestations are headache, hemiparesis, nausea, vomiting, vertigo, and gait disturbance. Children with GBM may present acute neurological deterioration from its rapid growth or intratumoral hemorrhage. Some of these symptoms were also observed in this case after the growth of GBM size.

Neuroimaging also plays an important part in the diagnosis and management of GBM. Computed tomography (CT) and magnetic resonance imaging (MRI) is commonly used to assess brain tumors. MRI precontrast and postcontrast provide finer detail and more anatomic information for surgery and radiotherapy planning. On precontrast T1 weighted, these tumors are isointense or hypointense. After contrast, T1-weighted sequences typically show rim contrast enhancement, with a thick irregular wall surrounding the non-enhancing area of central necrosis. T2-weighted and FLAIR sequences usually show a heterogeneous mass with variable signal intensity surrounded by a broad zone of peritumoral T2-hyperintensity (representing non-enhancing tumor component/ tumor infiltration). Magnetic resonance spectroscopy typically displays choline peak (an indicator of membrane cell turn-over), with reduced N-acetyl aspartate (an indicator of neuron viability) in the region of the tumor, also in peritumoral hyperintensity.

Pediatric GBMs are still a huge challenge to treat and a multidisciplinary approach is needed. Standard treatment guidelines are not available for pediatric GBM cases. Standard treatment of GBM in children is extrapolated from adult GBM. Standard care treatment is gross total resection or maximal safe resection followed by adjuvant treatment using chemotherapy and radiotherapy. Several studies found that gross total resection is a significant predictor of prolonged survival because it sets the stage for successful adjuvant therapy response.
Figure 5. Non-contrast head CT showed a significant reduction of left temporoparietal mass with minimal subdural fluid collection and pneumocephalus.

infiltrative nature of GBM warrants the need for adjuvant treatment to prevent recurrence post-surgery.17

GBM on the patient is also complicated by COVID-19. COVID-19 effects on cancer growth are still not well established. In this case, we observed this patient contracted mild COVID-19 with no severe symptoms. A few weeks after the COVID-19 resolution, the GBM doubled in size and caused severe symptoms in the patient. It may be incidental and it is still unclear whether this growth was caused by COVID-19. Because COVID-19 was recently discovered and we don't know much about its complication and interaction with other diseases.

SARS-CoV-2 penetrates olfactory mucosa and may enter the brain through the cribiform plate or the blood-brain barrier (BBB) because inflammatory cytokines induce BBB instability via monocytes.14,15 Astrocytes also possess ACE2 receptor capacity that could further spread the virus in the brain parenchyma.16 Neuropsychological symptoms observed in COVID-19 patients were hypothesized to be caused by brain inflammation triggered by increased vascular endothelial growth factor (VEGF).17 VEGF is also known to promote the proliferation of GBM stem-like cells.18 No clinical trial or case series is yet investigating the connection between GBM and COVID-19. But from this case, it may be worthwhile to investigate this matter further to understand better COVID-19 and how it affects GBM patients.

Glioblastoma is a rare disease that has multiple factors affecting its progression. This study did not account for other factors that may affect this disease, one of the limitations of this case study. This case report can't establish a cause-effect relationship between COVID-19 and glioblastoma. More study is needed to determine the cause-effect relationship.

CONCLUSION

Pediatric GBM is a rare disease compared with the adult counterparts. Even with modern technologies and varieties of treatment modalities, pediatric GBM is still a challenge to treat with an asymptomatic prognosis due to its infiltrative nature and high recurrence rate. The patient had an acute deterioration of the neurological condition and rapid growth of the tumor after he contracted COVID-19. Further observation will be required to determine if the rapid growth of GBM is associated with COVID-19.

CONFLICT OF INTEREST

All author declares no conflict of interest regarding the publication of the case report.

ETHICS CONSIDERATION

The patient’s guardian had received informed consent regarding publishing the patient’s medical data in a medical journal as a case report.

FUNDING

This case report doesn't receive any specific government or private sector grant.

AUTHOR CONTRIBUTION

All authors had contributed to the manuscript writing and agreed on the final version of the published case report.

REFERENCES


