Glioblastoma multiforme (GBM) is a rare, highly aggressive brain tumor associated with a poor outcome in both children and adults. Treatment usually involves a combination of surgical resection, chemotherapy, and radiotherapy, but ultimately it is incurable. Evidence suggests that congenital GBM may have a better prognosis with improved survival compared with GBM in older children. We describe the first known report of spontaneous resolution of a congenital GBM without any systemic therapy. A limited debulking procedure was performed at diagnosis, and the residual tumor underwent spontaneous resolution over the following 21 months. The patient remains in remission, with no tumor recurrence after 5 years of follow-up. Despite the tumor regressing, the patient has had an adverse neurologic outcome, with severe developmental delay and seizures. This case suggests that congenital GBM may be a separate biological entity much like neuroblastomas in infants, and therefore associated with better outcomes and even spontaneous resolution.

Anaplastic astrocytomas and glioblastomas (World Health Organization grade III and IV astrocytomas) account for 7.1% of all central nervous system tumors in children. Congenital brain tumors are rare, with an incidence of 3.6 to 4.1 per 100,000 births. There are no consensus definitions for “congenital” brain tumors. Jellinger and Sunder-Plassmann proposed a classification system for definitions of “congenital”: definitely congenital, producing symptoms at birth or within the first 2 weeks of life; probably congenital, producing symptoms in the first year of life; and possibly congenital, producing symptoms beyond the first year of life. In practice, GBMs in children under age 3 years are commonly referred to as “infant” GBMs, and “congenital” is reserved for those that occur within the first few months of life. Only 8.8% of congenital brain tumors receive a diagnosis of GBM (WHO Grade IV), the first case of which was reported in 1917 by Holt. In older children, GBM is an aggressive malignancy with a 3-year event-free survival rate of <10%, and they are highly resistant to treatment. Treatment involves a combination of surgical resection, chemotherapy, and focal radiotherapy, but almost all tumors recur and are ultimately incurable. In contrast, the outcome in congenital GBM is less clear. Although the literature comprises mostly case reports, there is a suggestion that congenital GBM carries a better prognosis if the patient survives the initial period of diagnosis. Although surgical resection alone is not considered to be curative, there is some evidence that congenital GBMs are sensitive to chemotherapy and that initial chemotherapy can make the GBM more amenable to successful surgical resection. We present here a case of congenital GBM that underwent spontaneous resolution of a congenital GBM without any systemic therapy; Ms. Tobias analyzed and reported on the original slides, approved the histopathology figures and legends, and critically reviewed the manuscript; Ms. Doyle created the histopathology figures and legends and critically reviewed the manuscript; Dr. Ziegler conceptualized and designed the project, provided feedback, and reviewed and revised the manuscript; Dr. Ellison reviewed the histopathology to assist with confirmation of the diagnosis, undertook molecular analysis of the tumour, and revised the manuscript; and all authors approved the final manuscript as submitted.

Dr. Davis collected the patient data, conducted the literature review, drafted the initial manuscript, and edited the manuscript according to feedback of the other authors; Dr. Ziegler conceptualized and designed the project, provided feedback, and reviewed and revised the manuscript; Ms. Doyle created the histopathology figures and legends and critically reviewed the manuscript; Ms. Tobias analyzed and reported on the original slides, approved the histopathology figures and legends, and critically reviewed the manuscript; Dr. Ellison reviewed the histopathology to assist with confirmation of the diagnosis, undertook molecular analysis of the tumour, and revised the manuscript; and all authors approved the final manuscript as submitted.

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spontaneous resolution after partial resection alone.

PRESENTATION

A 5-week-old boy presented to hospital for increasing head circumference, failure to thrive, irritability, and vomiting. He had been well until 2 weeks of age and then developed back arching, and from 3 weeks, he began vomiting after every feed. He was awake for only 60 to 90 minutes at a time and did not respond to voice or loud noises. On examination, he was noted to have macrocephaly (>97th percentile), dilated scalp veins, and a bulging tense fontanelle, and he was not fixing and following. He had a brisk, symmetrical Moro reflex and bilateral brisk knee jerks. Pupils were symmetrical and reactive. A head ultrasound showed markedly enlarged lateral and third ventricles and a 7-cm, complex cystic and solid mass in the medial aspect of the left temporal horn. Computed tomography and MRI confirmed marked dilatation of the lateral, third, and fourth ventricles, with a heterogenous, partially calcified complex mass lesion in the left cerebral hemisphere (Fig 1).

The same day, the patient had an emergency ventricular tap, and the following day, he had a single burr hole craniotomy and debulking of the tumor. There was significant intraoperative bleeding that was well controlled with Surgiflo and Gelfoam. He had recurrent seizures in the postoperative period and was commenced on midazolam and phenytoin. Histopathological evaluation showed the features of a GBM (WHO grade IV; Fig 2), with frequent mitoses, palisading necrosis as well as extensive areas of geographic necrosis, and prominent microvascular proliferation. There was limited infiltration of adjacent parenchyma. Immunohistochemistry supported the diagnosis. Tumor cells showed limited immunoreactivity for GFAP, but all expressed OLIG2 and MAP2. There was also universal expression of INI1. There was no immunoreactivity for synaptophysin, neurofilament proteins, or NEUN among tumor cells. The growth fraction of the tumor, as estimated by Ki67 immunolabeling, was high at 60% to 70%. ATRX expression was preserved, and variable nuclear immunoreactivity for P53 among scattered tumor cells matched the pattern seen when TP53 is wild type. No amplification of EGFR, PDGFRA, MET, or CDK4/6 and no rearrangement of NTRK1/2/3, MYB, or BRAF were detected by interphase fluorescence in situ hybridization. There was also no duplication of BRAF to suggest the presence of a KIAA1549-BRAF fusion gene. Sequencing analyses showed no mutation of H3F3A at the G34 or K27 codons, and there was no mutation of BRAF at the V600 codon or across the FGFR1 hotspot. No duplication of the FGFR1 tyrosine kinase domain was detected. Postoperative MRI showed a large amount of residual tumor (Fig 3) and no significant areas of hemorrhage.

Because of the size of the tumor, and the likely severe impact on development, the decision was made not to insert a shunt and to offer palliative care. No radiotherapy or chemotherapy was administered,
and an end-of-life care plan was developed.

The patient had another presentation to hospital with increased seizures and consequently had a palliative ventriculoperitoneal shunt inserted at 4 months of age. Follow-up brain MRIs at 9 months of age showed a reduction in the size of the tumor. A brain MRI at 15 months of age showed complete resolution of the tumor (Fig 4).

This patient is now 5 years old, and there has been no tumor recurrence. However, his MRI shows markedly abnormal residual brain, and he has multiple asymmetric seizures each day. He has an asymmetric spastic quadriplegia with severe developmental delay.

**DISCUSSION**

This case of spontaneous resolution of a congenital GBM without adjuvant chemotherapy or radiotherapy, suggests that some congenital GBMs may be a distinct clinicopathological entity with a previously undescribed potential for spontaneous resolution.

GBM is a highly aggressive malignancy with a poor prognosis in adults and children. It rarely occurs during infancy, which limits our understanding about the disease in this age group, and is even less common in newborns. However, the accumulated data suggest that GBM in young children, including infants and newborns, has a different biology, possibly with improved clinical outcomes.17 This case adds to the literature and, to our knowledge, is the first reported case of a spontaneous resolution of a congenital GBM.

There is some evidence that congenital and infant GBMs may have a different molecular genotype compared with the same tumor in older patients. Gielen et al18 recently evaluated 35 cases of infant GBM, including 8 cases of congenital GBM. They found significantly lower rates of genomic alterations in the infant and congenital cases compared with older children with GBM. For example, they described fewer chromosomal changes, a complete absence of EGFR or PDGFRA amplifications, rare cases of CDKN2A loss (and then only occurring in the older infants), and only 2 patients with H3.3K27M mutations and 2 with BRAFV600E mutations. Similarly, Batra et al19 found that GBMs arising in infants <3 years of age were significantly less likely to harbor TP53 mutations than children aged 3 to 6 years (28% vs 70%). This is consistent with the findings in the case reported here, in which we did not identify any genetic alterations that are reported commonly in GBMs from older children. Spontaneous tumor resolution is seen in other congenital tumors, most commonly in neuroblastoma. Neuroblastomas also carry a better prognosis in children under age 18 months, and there is a well-recognized outcome of spontaneous regression in this age group, even when the patient has metastases at initial diagnosis.20 This case report suggests that some examples of congenital GBM may have a distinct biology compared with GBM that occurs in older children, leading to a distinct clinical phenotype, just as congenital neuroblastoma is a distinct entity with a unique propensity to resolve spontaneously.

The possibility of a unique biology for congenital GBM is supported by the improved outcomes reported in this age group. Sanders et al retrospectively reviewed 16 young patients with high-grade astrocytomas and found that of the 4 cases of congenital GBM, all were still alive at the time of publication, with 3 having reached 5 years of age.21 The Pediatric Oncology Group experience also suggests that those infants with GBM respond better to chemotherapy and have a better overall survival compared with older children and adults.17 Their study demonstrated an overall survival of 50% at 5 years.

Although some children with congenital GBM may have improved outcomes, the optimal treatment remains controversial. In older patients with glioblastoma, the goal of surgery is to achieve gross total resection (GTR) of the tumor because the extent of resection correlates with longer progression-free survival.22,23 However, achieving GTR is particularly challenging in young children.24 The tumors are often large, resulting in fragile overlying vasculature, which can be difficult to identify and can easily tear and collapse.25 Other factors such as limited circulating blood volume and intricacy of the surgery, limit the ability to achieve GTR in young patients. Although infants who did not have any surgery had a poor survival (average 2.3 months), the case report described here suggests that achieving GTR may not be as important in young children.15

Optimal treatment after surgery is unclear. Radiotherapy is the standard treatment postsurgery and plays an important role in delaying progression in older children26; however, it is almost always avoided in congenital GBM because of the unacceptable long-term toxicities.14 There is no consensus on the benefit of chemotherapy in congenital GBM.
GBM, but some reports suggest that it offers an improved outcome.\textsuperscript{14} Kotecha et al described 2 cases in which chemotherapy before surgery allowed for gross total resection where it had been previously technically impossible.\textsuperscript{15} However, our case raises the possibility that tumor shrinkage may occur independently of chemotherapy and that better outcomes may relate to the underlying biology, rather than the treatment implemented. There are 2 other individual case reports of patients who survived with congenital GBM and had had surgery alone with no chemotherapy or radiotherapy. One was diagnosed at birth, had a surgical resection alone of a frontal lobe GBM, and showed no evidence of malignancy at 2.5 years postsurgery.\textsuperscript{15} The other was diagnosed at 30 weeks' gestation, had surgical resection alone of a cerebral hemisphere tumor, and was alive at 5 years postsurgery.\textsuperscript{27}

Despite potentially improved overall survival in congenital GBM, there can be significant long-term complications and a poor neurologic outcome, as in the case discussed here. Young children with GBMs have generally been reported to have severe developmental sequelae, and seizure disorders. Forty-four percent of these patients were not able to attend school, and of those who were, most had a mild to moderate intellectual disability.\textsuperscript{21} They were also reported to have endocrinopathies including growth hormone deficiency, thyroid deficiency, precocious puberty, and adrenocortical deficiency. Batra et al\textsuperscript{19} reported data from the Children's Cancer Group CCG-945 trial in which they compared neuropsychological outcomes in children <3 years of age with GBM with those aged 3 to 6 years. Despite the fact that 90% of the infants with GBM did not receive cranial irradiation, they had significantly impaired measures of intelligence, visual-motor integration, and visual memory and processing speed, with lower scores than those obtained by the older children treated with irradiation. The mean IQ score for the infants after treatment of GBM was 70, which is significantly lower than the normal population.

Despite having limited surgery and no additional antitumor therapy, our patient has severe neurologic impairment and refractory epilepsy. This suggests first that the tumor itself may cause significant long-term morbidity, although the initial surgery may have also contributed to the poor neurologic outcome. Second, this case highlights a situation in which therapies that may cause further damage in patients who are already at high risk of severe neurologic impairment could be avoided.

CONCLUSIONS

GBM is a rare, aggressive tumor with a poor outcome in older children despite treatment with surgery, chemotherapy, and radiotherapy.\textsuperscript{8} Congenital GBM is thought to have a distinct phenotype with improved clinical outcomes. We have described the first reported case of a congenital GBM that has undergone spontaneous resolution. This suggests that congenital GBM is a distinct disease entity with unique biological characteristics and a previously undescribed potential for regression that is independent of further treatment with chemotherapy or other treatment modalities. Despite the potential for improved survival in congenital GBMs, this case demonstrates that patients may still have a poor neurologic outcome because of the mass effect of the original lesion.

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The authors received informed consent from the child’s parents to describe this patient for a case report.

ABBREVIATIONS

GBM: glioblastoma multiforme
GTR: gross total resection
WHO: World Health Organization

REFERENCES


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