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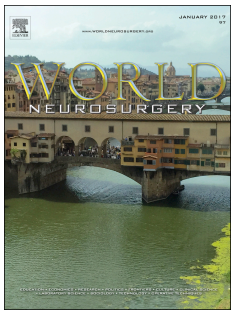

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Congenital glioblastoma multiforme with long-term childhood survival: a case report and systematic review

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AUTHOR CONTRIBUTION:
Dr. Espiritu was involved in the acquisition of data, analysis and interpretation and writing of the initial and final draft of the manuscript for intellectual content.

Dr. Terencio was involved in the study conception, acquisition of data, analysis and interpretation, critical revision of the manuscript for intellectual content and study supervision.

Dr. Jamora was involved in the study conception, acquisition of data, analysis and interpretation, critical revision of the manuscript for intellectual content and study supervision.

ABSTRACT

Background: Congenital glioblastoma multiforme (cGBM) is an infrequent primary central nervous system tumor occurring within the first few months of life with a reported poor overall prognosis.

Objective: To describe our own clinical case of cGBM and review the literature with prolonged survival.

Methods: We report our case of cGBM with prolonged survival at 4 years. A systematic review was conducted on cases of cGBM with long-term childhood survival. We searched online databases until August 2019 for relevant articles.

Results: Our patient underwent an emergency right hemicraniectomy with excision and biopsy of the right cerebral hemisphere mass and insertion of a ventriculoperitoneal shunt. At present, she is a 52-month-old child with good speech and minimal left hemiparesis and able to ambulate, with a Functional Independence Measure (WeeFIM) score of 109. Out of 160 articles screened, there were 10 articles included. A total of 15 patients, including our case, were analyzed qualitatively. The age at presentation ranged from 30 weeks age of gestation to 35 days. Most patients underwent surgical excision (86.7%) and adjuvant chemotherapy (66.7%). The reported range of survival of these patients was from 27 to 110 months.

Conclusions: Limited evidence from 15 cases of cGBM suggests that surgical excision and/ or chemotherapy may prolong the survival of patients. Therefore, these interventions may be offered and performed to patients with cGBM on a case-by-case basis. Larger clinical studies or registry-based information are necessary to substantiate the implications of our review.

1 BACKGROUND

Congenital central nervous system tumors occur in 1.1-3.6/100 000 newborns.[1] In particular, congenital glioblastoma multiforme (cGBM) is an remarkably infrequent primary brain tumor [World Health Organization (WHO) Grade IV] which is detected within the first few months of life.[2,3] Typical histopathological findings of this tumor include infiltrative, densely cellular, with high mitotic activity, marked cytoplasmic and nuclear pleomorphism, presence of areas of necrosis and vascular proliferation with immunohistochemical positivity for glial fibrillary acidic protein (GFAP).[3] Most recent epidemiological data from the Central Brain Tumor Registry of the Unites States (CBTRUS) during 2011 to 2015 showed that there was an increasing trend of average annual age-adjusted incidence rates per 100,000 population for glioblastoma, as follows: 0.12 (0 to 4 years), 0.17 (5 to 9 years), 0.20 (10 to 14 years), 0.53 (15 to 39 years), 6.93 (≥ 40 years).[4] Similar to the adult GBM, the overall prognosis of cGBM is poor.[5] The reported percentage of stillborn or dead within the first 24 hours is 29%, 2-month mortality at 56%, and 1-year mortality at 64%.[3]

On the contrary in this report, we present an exceptionally rare case of cGBM with an unexpected good survival outcome after surgical removal of the tumor. She is alive at 4 years of life capable of ambulation with only minimal left hemiparesis. Moreover, a systematic review of cases of cGBM with long-term survival was conducted with an aim to describe and assess their clinical characteristics and the forms of interventions they received that may had contributed to the longer survival in these patients.

2 CASE PRESENTATION

A 4-week old, Filipino female was brought to the clinic due to increased head size. She was born full-term by vaginal delivery at the hospital with no antenatal and fetal-maternal complications. The family history was noncontributory. At birth, her head circumference, weight and length were 35.5 cm (z-score > 1), 3680 grams, and 56 cm, respectively. One week prior to admission, her parents noticed patient's head size to be enlarging associated with multiple bouts of nonprojectile vomiting. At admission, she was active, irritable with note of bulging anterior fontanels, splayed cranial sutures and head circumference at 40 cm (z-score > 3) with spontaneous movement of all extremities. A pre-operative magnetic resonance imaging (MRI) scan displayed a large, complex, solid, faintly enhancing intracranial mass at the right cerebral hemisphere measuring 11.0 x 7.4 x 9.1 cm (anteroposterior x width x craniocaudal) with cystic intensities and areas suggestive of hemorrhage. The mass caused subfalcine herniation to the left, descending uncal herniation on the right side, midline shift to the left with narrowing of the right lateral ventricle and third ventricle and secondary dilatation of the left lateral ventricle (see Figure 1A to D). A high-grade glioma was highly suspected based on these radiologic findings.

Medical decompression using mannitol, hypertonic lactate solution and acetazolamide were immediately administered. A multidisciplinary team composed of a pediatric neurologist, general pediatrician, neonatologist and pediatric neurosurgeon was formed. A decision to perform an emergency right hemicraniectomy with excision and biopsy of the mass, and insertion of ventriculoperitoneal shunt was reached. During the procedure, only an approximately 60% of the mass was resected due to significant profuse bleeding with an estimated blood loss of 500 mL. Intraoperatively, appropriate amounts of packed red blood cells aliquots were transfused. The patient was initially observed at the neurology intensive care unit. A second-look surgery was

planned but these were not performed due to financial constraints. During this admission, however, she developed hospital-acquired pneumonia and peripherally inserted central catheter-associated infection and was subsequently administered with culture-guided antibiotics. She stayed at the hospital for 5 weeks and was then discharged awake and with good suck and activity.

Biopsy of the mass revealed sections showing brain tissue diffusely infiltrated by tumor cells with fibrillary process and tumor cells with ovoid eosinophilic cytoplasm. Mitotic figures were abundant and microvascular proliferation and tumor necrosis were present (see Figure 2). Immunohistochemistry showed positivity for glial fibrillary acidic protein (GFAP), vimentin, INI-1, p53 in majority of tumor cells, weak membrane positivity in moderate number of tumor cells for epithelial membrane antigen, and negativity for synaptophysin in tumor cells. These histopathologic and immunohistochemical findings supported the diagnosis of a high-grade glioma consistent with a diagnosis of glioblastoma, WHO Grade IV.

Postoperative plain cranial computed tomography (CT) scan showed a reduction of the size mass measuring 3.4 x 2.0 x 3.5 cm, with significant regression of the previously noted severe mass effects and herniation (see Figure 1E to F).

Clinical and radiological monitoring twice a year and adjuvant chemotherapy were appropriately considered and advised. After informed discussion with the family, close observation of clinical signs indicating tumor recurrence was done alone and chemotherapy was deferred due to significant financial difficulties. The patient had an auspicious follow-up in the outpatient clinic in the interim. At present, the patient is a 52-month-old child with good speech and minimal left hemiparesis and able to ambulate. Our patient has a Functional Independence Measure

(WeeFIM) score of 109 (maximum score, 126), indicating that the patient is independent in the following six domains: self-care, sphincter control, transfer, locomotion, communication and social cognition.

3 SYSTEMATIC REVIEW

We included case reports/ series involving patients with cGBM who were detected within the first two months of life in accordance with the most accepted and current classification system.[2,3] We included patients with long-term survival which was defined in this review as patients who reached a survival for at least 24 months, the age start for "childhood" stated by the American Academy of Pediatrics.[6] We searched the following electronic databases until August 2019 for relevant articles: PubMed by MEDLINE, CENTRAL by The Cochrane Library, Scopus, LILACS, and HERDIN. General search terms employed were "congenital" and "glioblastoma multiforme". We screened all the titles and abstracts of records retrieved from the systematic search. All articles which satisfied the screening criteria were obtained in full-text. The articles which fulfilled the eligibility criteria were included in this review (see Figure 3). The following data were collected: age, sex, clinical presentation, location of the mass, biopsy results, interventions done, and survival outcomes. Descriptive statistics was used to synthesized the data.

4 RESULTS

Out of 160 records retrieved from the systematic search, 10 articles involving 14 patients with cGBM with long-term survival reaching childhood were included in this review (see Table 1). [1,5,7–14] Including our present case, information from a total of 15 patients were synthesized in this review.

Age at presentation ranged from 30 weeks age of gestation, which was detected using antenatal fetal ultrasound, to 35 days, with a female:male ratio of 3:4. Most patients including our case (13/15 patients; 86.7%) underwent some form of surgical excision, either total or partial resection.[1,5,7–13] Several patients (10/15 patients; 66.7%) underwent any adjuvant chemotherapy.[1,5,9–12,14] Typical chemotherapeutic regimen administered to the patients include varying combinations and number of courses of vincristine, etoposide, cisplatin, carboplatin, methotrexate, cyclophosphamide, isophosphamide, nimustine, thiotepa, melphalan and prednisolone.[1,5,9–12,14] A single patient underwent whole brain irradiation with a dose of 54 Gy which was administered during the second year of life.[9] The reported range of survival of included patients were from 27 to 110 months. Most patients were reported to have survived from 24 to 60 months (10/15 patients; 66.7%) and fewer patients (5/15 patients; 33.3%) survived for more than 60 months.

5 DISCUSSION

This current case study and systematic review presented the most extensive search for cases of cGBM who had relatively good survival outcomes, with usable information from a total of 15 patients.

Available data from this review showed that patients who underwent surgical resection of the tumor and chemotherapy may be beneficial to prolong the survival of patients with cGBM. According to other reports, the mortality of patients who received any combination of tumor-targeted treatments, which included surgical intervention chemotherapy radiotherapy, at 2 months and at 1 year were reported to be at 25% and 63%, respectively.[3] On the other hand,

patients who did not received any form of tumor-targeted therapies had worse prognosis with the mortality rate at 2 months and at 1 year reported at 97% and 100%, respectively.[3]

The congenital form of GBM seemed to have a distinctive genetic feature that is different compared to the pediatric (pGBM) and adult types (aGBM). Mutations in TP53 gene and overexpression of nuclear P53 were found in pGBM patients ages greater than 3 years old and were associated with adverse progression-free survival and overall survival.[15,16] While epidermal growth factor receptor (EGFR) amplification and phosphatase and tensin homolog (PTEN) deletions less frequent in pGBM, modifications in the expression of EGFR, PTEN including platelet-derived growth factor receptor (PDGFR), INK4a/ARF, isocitrate dehydrogenase 1 (IDH1) and TP53 were more common in aGBM.[17–26] In cGBM, EGFR and PDGFR α-type amplifications, PTEN mutations including p16/CDKN2A deletions were not demonstrated.[1] Gene expression for EGFR and PDGFRα in cGBM were also found to be lower compared to pGBM.[11] Interestingly, most patients with cGBM revealed p53 immunoreactivity (as seen in our own case) but with no TP53 mutation, which may suggest presence of other unidentified mechanism for overexpression.[1,3] The current literature supports p53 pathway dysregulation in the formation of cGBM.[1,3,8,11,27,28]

While radical resection was suggested in older pediatric patients with GBM because this intervention was associated with longer progression-free survival, the performance of this strategy in younger children may be challenging.[13,29–31] Apart from the typically massive size of the tumor, the limited circulating blood volume and complexity of the surgery may preclude gross total resection in young children.[11,13] Serious intracranial hemorrhage may also occur postoperatively because these tumors are highly vascularized and susceptible to massive

bleeding.[3,11] Therefore, aggressive surgery may not be always essential since it could lead to increased morbidity.[11] In our described patient, severe intraoperative bleeding prevented gross total resection of the tumor; however, despite partial resection, good functional outcomes and long-term survival were achieved. Therefore, our case provides an evidence that partial resection, as reported in another case, may be a viable option especially if lowered risks for intra- and post-operative complications are desirable.[13]

Some evidence from case reports suggests that chemotherapy and radiotherapy may aid in lengthening the survival of patients with cGBM. Various combinations and phases of platinum-based antineoplastic drugs such as carboplatin and cisplatin, topoisomerase II inhibitor etoposide, alkylating agents which include cyclophosphamide, ifosfamide, thiotepa, melphalan and nimustine, and the antimetabolite methotrexate were previously utilized with varying survival outcomes.[1,5,9,11,14,32,33] A tumor dose of 40 Gy and whole-brain irradiation of 54 Gy were attempted in two separate case reports.[9,34] Based on the available evidences, surgical excision with adjuvant chemotherapy for cGBM may be the most appropriate strategy and radiotherapy is reserved for refractory cases.[3] However, as pointed out in our own patient, performing surgical resection without chemotherapy may be a feasible choice particularly in cases where financial limitation is a tangible and substantial matter.

The presented survival and mortality outcomes data for patients with cGBM in this review are not sufficient to conclude the effectiveness of the existing interventions due to lack of evidentiary support from clinical trials. Information on other important critical outcomes such as functional or neurological disability, development and cognitive outcomes, and quality of life, are lacking in the cases presented and therefore, these endpoints should be carefully addressed individually in patients with malignant brain tumors and future researches.[35]

Surveillance for tumor recurrence among cGBM patient post-excision may warrant both clinical and radiographic data obtained at regular intervals due to the unpredictable biological behavior of the mass. Reappearance of tumor may be evident in the imaging without guidance from emergence of new neurological signs. However, pecuniary considerations largely influenced the informed decision of the family that imaging procedure shall be performed as new clinical signs develop, including their preference to forego the second-look surgery and chemotherapy. This is understandable particularly in the Philippine setting where medical cost trend rate was considered seriously high and out of pocket health expenditure was tremendously significant at 56.7%.[36,37]

Currently, there are no consensus guidelines on the provision of neurosurgical, neurooncological and radiation-oncological care for patients with cGBM. Indeed, modern surgical interventions and several chemotherapeutic and radiotherapy regimens are currently available which could possibly prolong patients' survival. However, in order to develop appropriate guidelines for the management of this malignant tumor, the following major issues should be pursued: (1) Appropriate patient selection based on certain clinical characteristics that will benefit from a specific intervention; (2) Suitable surgical procedure (either total, near total or subtotal resections) for a particular patient; (3) Appropriate choice of chemotherapeutic agents; (4) Utility of radiotherapy.

6 CONCLUSIONS

The limited evidence from case reports included in this review suggests that surgical resection, chemotherapy and possibly radiotherapy may substantially lengthen the survival of patients with cGBM. The results of our review should encourage clinicians to put forth informed treatment decisions based on the individual characteristics and risk and benefits of the intervention. Undeniably, the tremendous rarity of this tumor might preclude us from conducting prospective clinical studies which will directly compare existing interventions with potential beneficial outcomes. However, larger prospective clinical trials, or registry-based data are still crucial to ascertain the role of these interventions for cGBM.

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8 ACKNOWLEDGMENT

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ABBREVIATIONS:
cGBM – congenital glioblastoma multiforme
pGBM – pediatric glioblastoma multiforme
aGBM – adult glioblastoma multiforme
WHO – World Health Organization
GFAP – glial fibrillary acidic protein
MRI – magnetic resonance imaging
WeeFIM – Functional Independence Measure
EGFR – epidermal growth factor receptor
PTEN – phosphate and tensin homolog
PDGFR – platelet-derived growth factor receptor
IDH1 – isocitrate dehydrogenase 1

HIGHLIGHTS

- cGBM is an extremely rare tumor with a reported overall poor prognosis.
- We report a cGBM case that underwent surgery and alive at 52 months.
- Fifteen cGBM cases with extended survival were pooled in this review.
- Surgical excision-only approach may be a viable option in cases with financial limitation.
- Limited evidence showed that surgery with chemotherapy may be the best strategy for cGBM.

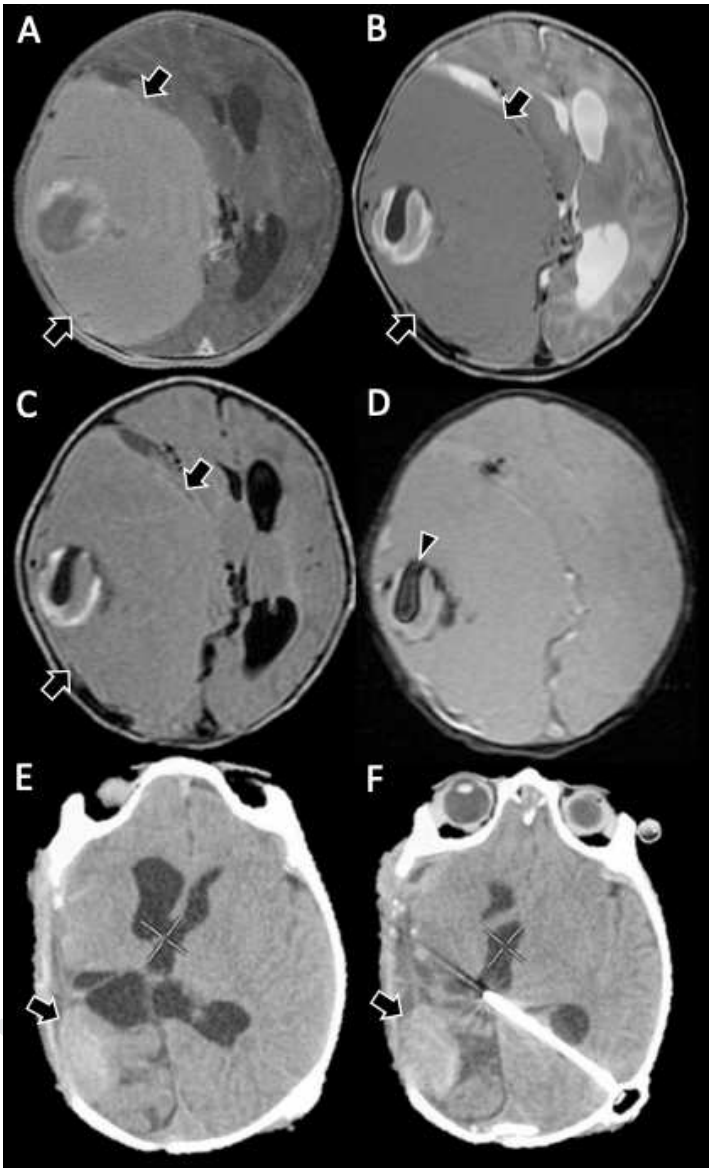

Figure 1. Axial view of the preoperative cranial magnetic resonance imaging (MRI) and postoperative plain cranial computed tomography (CT) scan of the patient (selected images).

A large, solid, faintly enhancing tumor (pointed by the arrows; A, T1-weighted image with gadolinium enhancement; B, T2-weighted image; C, fluid attenuated inversion recovery image) was seen at the right cerebral hemisphere measuring 11.0 x 7.4 x 9.1 cm (anteroposterior x width x craniocaudal) causing severe mass effects, midline shift to the left and subfalcine herniation. There were cystic intensities inside the mass with areas suggestive of hemorrhage; D, gradient echo image, arrowhead. Postoperatively, there was an interval decrease in the size of the mass, measuring 3.4 x 2.0 x 3.5 cm; E to F, arrows. A left sided ventriculoperitoneal shunt is shown, with its tip in the region of the right lateral ventricle; F.

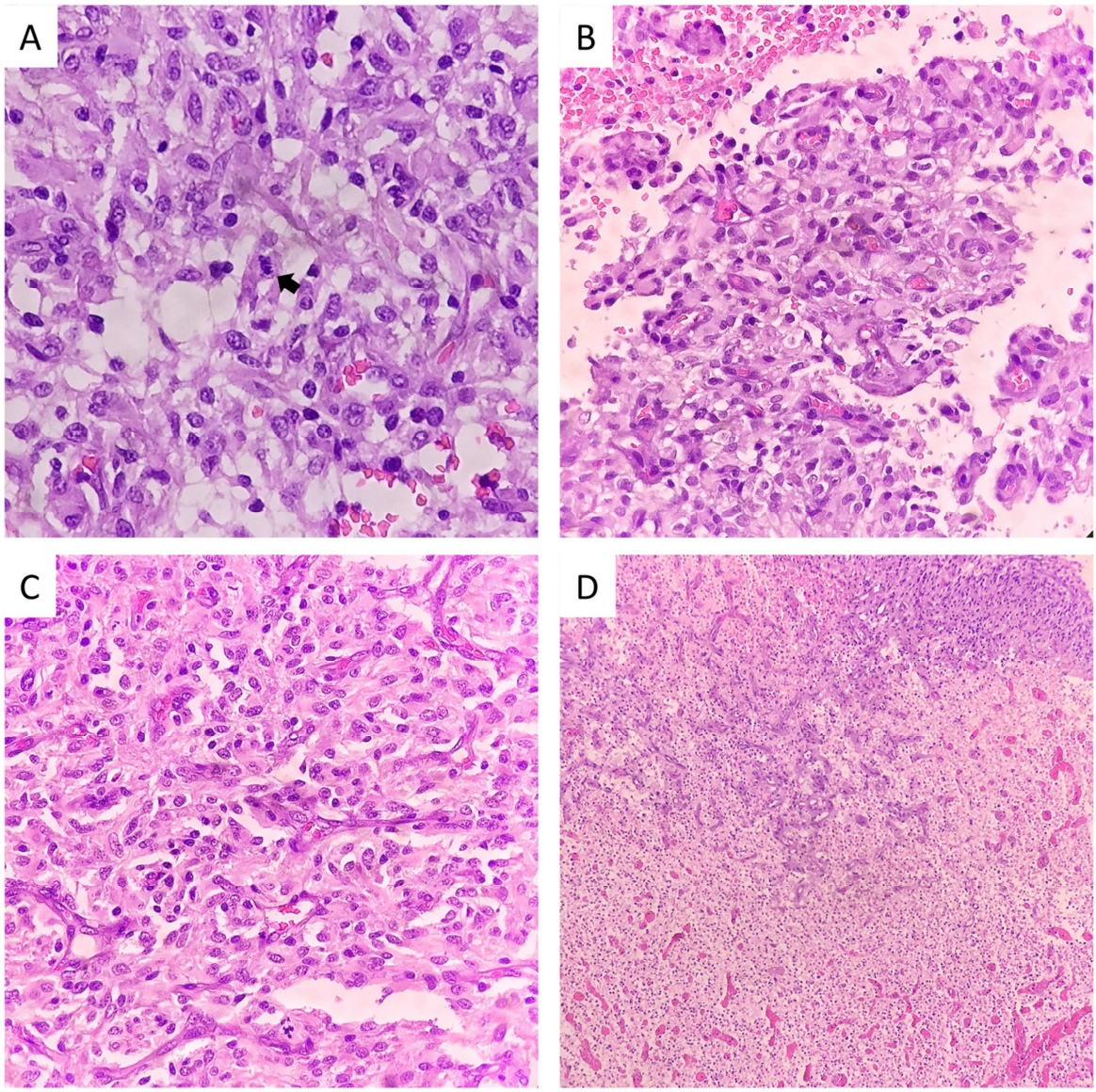

Figure 2. Histopathologic sections of the right cerebral hemisphere tumor displaying features of glioblastoma multiforme (Hematoxylin-eosin stain).

The images show the following features: (A) A mitotic figure (black arrow); (B) Microvascular proliferation; (C) Tumor cells with ovoid eosinophilic cytoplasm; and (D), Tumor necrosis.

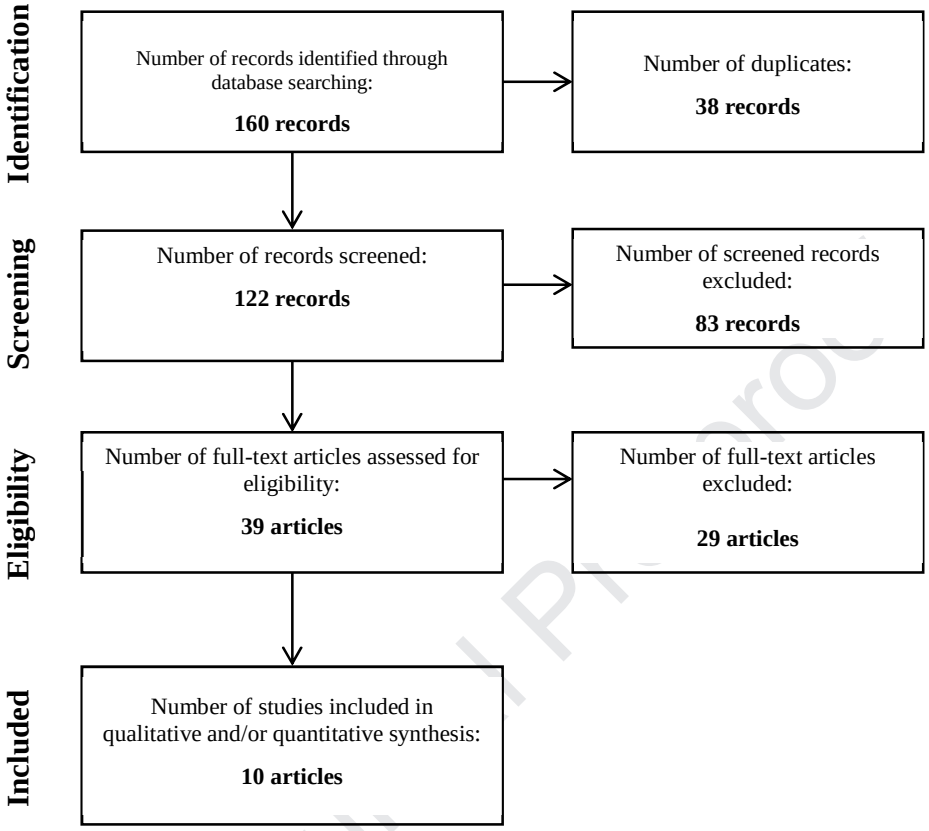

Figure 3. The PRISMA flow diagram for this review.

Table 1. Cases diagnosed with congenital glioblastoma multiforme with long-term survival of more than 2 years.

Reference	Age at Presentation	Sex	Clinical Presentation	Location of the Mass	Management	Outcome, in months
Alvarez, et al. 1987 (7)	30 weeks gestation	F	NR	NR	Surgical resection	Alive at 60
Winters, et al. 2001 (8)	1 day	M	Bulging fontanel, difficulty feeding, seizures	Frontotemporal lobe	Surgical resection	Alive at 30
Shimamura, et al. 2003 (9)	1 day	F	Weak cry, weakness, bulging anterior fontanel	Left parahippocampal gyrus and parietal lobe	Multiple surgical resections; chemotherapy; radiotherapy	Dead at 27
Baeesa, et al. 2007 (10)	7 days	M	Poor feeding, difficult to control seizures	Left temporal lobe	Surgical resection; chemotherapy	Alive at 72
Brat, et al. 2007 (1)	6 days	M	Seizures	Left parietal lobe	Surgical resection; chemotherapy	Alive at 67
	7 days	M	Bulging fontanel, irritability	Right cerebral hemisphere	Surgical resection	Alive at 90
	6 days	M	Hypothermia	Hypothalamus	Chemotherapy	Dead at 78
Macy, et al. 2012 (11)	1 month	M	NR	Right temporal-parietal lobes	Surgical resection; chemotherapy	Alive at 110
	14 days	F	NR	Right thalamus with intraventricular extension	Surgical resection; chemotherapy	Alive at 40
	6 days	F	NR	Septum pellucidum with intraventricular extension	Surgical resection; chemotherapy	Alive at 31
Jurkiewicz, et al. 2012 (12)	4 days	F	NR	Supratentorial region	Surgical resection; chemotherapy	Alive at 40
Boukas, et al. 2012 (5)	28 days	F	Seizure, vomiting, mild left sided weakness, head enlargement	Right frontal-parietal lobe	Surgical resection; chemotherapy; cystoventriculostomy	Alive at 30
Davis, et al. 2016 (13)	35 days	M	Head enlargement, failure to thrive, irritability, and vomiting, seizures	Left cerebral hemisphere	Ventricular tap; surgical resection; ventriculoperitoneal shunt	Alive at 60
Mandel, et al. 2016 (14)	1 day	M	Pallor, hypotonia, bradycardia, no spontaneous breathing, hypothermia	Bilateral frontal lobes	Chemotherapy	Alive at 36
Espiritu, et al. 2020 (Present Case)	21 days	F	Head enlargement, vomiting, seizures	Right cerebral hemisphere	Surgical resection; ventriculoperitoneal shunt	Alive at 52

F, Female; M, Male; NR, Not reported.