Radiological features of infantile glioblastoma and desmoplastic infantile tumors: British Columbia's Children's Hospital experience

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OBJECT Two of the more common infantile brain tumors, glioblastoma multiforme (GBM) and desmoplastic infantile tumors (DITs), can be difficult to distinguish on MRI. Both tumors occur in the supratentorial compartment and both have solid and cystic components. Differentiating between the 2 on MRI studies could assist the surgeon in discussions with family and child management. The authors report on their institutional experience with both tumors, focusing on radiographic features, especially the diffusion studies, which might be useful in distinguishing between infantile GBM and DIT.

METHODS A retrospective review was undertaken of all infantile brain tumors treated at British Columbia's Children's Hospital between 1982 and 2012, and cases of GBM and DIT were recorded. Only cases that had imaging were included in the study. A literature review was completed to identify reported cases of infantile GBM and DIT. Only reports that described or included radiological studies (particularly MRI) of the tumors were included. Certain radiographic features of the tumors were reviewed, including location, size, consistency, pattern of enhancement, and features on MR diffusion studies.

RESULTS Of 70 cases of infantile brain tumors, 2 GBM cases and 3 DIT cases (all 3 of which were desmoplastic infantile gangliogliomas [DIGs]) met the inclusion criteria. The radiological studies obtained in all 5 cases were reviewed by a neuroradiologist. All 5 patients had supratentorial tumors with cystic-solid consistency. Diffusion MRI studies showed restricted diffusion in the 2 GBM cases, but no evidence of restricted diffusion in the DIG tumors. The GBM tumors were heterogeneously enhancing, and the DIG tumors showed avid and homogeneous enhancement. The literature review revealed 29 cases of infantile GBM and 32 cases of DIG/DIT that met the inclusion criteria. The tumors were large in both groups. The tumors were cystic-solid in consistency in 10 of 30 (33%) of GBM cases and 28 of 32 (87.5%) of DIT cases. The contrast enhancement was heterogeneous in 9 of 30 (30%) GBM cases, and it was homogeneous and avid in 27 of 32 (84%) of DIT cases. Diffusion studies were recorded in 2 published infantile GBM cases, and in both of them diffusion was restricted. The authors only found 1 report that discussed DIG tumor features on MR diffusion studies, but the interpretation was difficult and unclear.

CONCLUSIONS Magnetic resonance imaging, especially diffusion-weighted imaging, may be a useful aid in distinguishing between infantile GBM and DIT tumors, with infantile GBM demonstrating restricted diffusion.

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KEY WORDS infantile glioblastoma; desmoplastic infantile ganglioglioma; desmoplastic infantile astrocytoma; congenital brain tumors; brain magnetic resonance imaging; diffusion; oncology

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ABBREVIATIONS ADC = apparent diffusion coefficient; BCCH = British Columbia's Children's Hospital; DIG = desmoplastic infantile ganglioglioma; DIT = desmoplastic infantile tumor; DWI = diffusion-weighted imaging; GBM = glioblastoma multiforme; GFAP = glial fibrillary acidic protein; PNET = primitive neuroectodermal tumor.

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BRAIN tumors are the second most frequent type of cancer occurring in children. The peak age of incidence in children is between 5 and 8 years.^{25,28} Between 1.3% and 11% of pediatric brain tumors occur in the 1st year of life, with the majority of tumors occurring supratentorially.^{5,17,25,28,33} The pathological types of infantile brain tumors include malignant tumors such as primitive neuroectodermal tumors (PNETs), atypical teratoid and rhabdoid tumors, and glioblastoma multiforme (GBM). However, benign tumors such as desmoplastic infantile tumors (DITs)—i.e., desmoplastic infantile ganglioglioma (DIG) and desmoplastic infantile astrocytoma—do occur in infancy. Prognosis depends on the tumor pathology, with malignant tumors almost universally doing poorly with respect to both mortality rates and long-term outcome of survivors.¹³ If it was possible to predict with high certainty the pathological features of an infantile brain tumor based on radiographic findings and, in particular, whether the tumor was malignant, this could assist in discussions with the family and the management of the child.

On standard T1- and T2-weighted MRI scans performed with and without contrast, 2 of the more common supratentorial infantile tumors (namely GBM, which is highly malignant, and DIG/DIT, which is benign) may be difficult to distinguish. Both tumor types may demonstrate solid and cystic components, with irregular enhancement, peritumoral edema, and apparent invasion of adjacent brain. Although diffusion-weighted imaging (DWI) is often performed in the assessment of brain tumors, the diffusion characteristics of these infantile tumors have been reported rarely in the literature.

We hypothesized that DWI would show restricted diffusion in the solid components of infantile GBM, but either no restriction or increased diffusion in the infantile DIG. The purpose of this study was to review the MRI features of both tumors, with attention to the diffusion imaging to see if the findings on diffusion MRI scans could distinguish between the 2 tumor types.

Methods

A retrospective review of the prospectively maintained neurosurgery and brain tumor databases at British Columbia's Children's Hospital (BCCH) and the British Columbia Cancer Agency was done to identify infantile brain tumors diagnosed between 1982 and 2012. Infants were defined as patients younger than 1 year at the time of diag-

nosis. From the total list of infantile brain tumors, cases of infantile GBM, DIG, and DIT were extracted.

For patients to be included in this study, they had to have a pathologically confirmed GBM (WHO Grade IV), DIG, or DIT (both WHO Grade I) and have undergone MRI (including DWI) as part of their evaluation. The patient's clinical presentation, neuroradiological studies, and individual treatments, including surgical intervention, chemotherapy, and radiation therapy, were recorded. The radiology reports were reviewed. In addition, the radiological studies were re-reviewed for this study by 2 neuroradiologists at BCCH. Factors on imaging that were reviewed included the following: tumor location, tumor size, presence and size of cyst, contrast-enhancement pattern, and presence or absence of restricted diffusion on MRI diffusion studies, with restricted diffusion defined as a reduction in apparent diffusion coefficient (ADC) values in the lesion by greater than 10% when compared with normal contralateral parenchyma.

The diagnosis of GBM, DIG, and DIT was based on the WHO 2007 classification of CNS tumors. All slides were reviewed, which included immunohistochemistry, to exclude alternative diagnoses.

A literature review of all published case reports and series of infantile and congenital GBM and DIG/DITs was undertaken through a search. Key words used included glioblastoma, infants, GBM, desmoplastic infantile tumors, DIG, desmoplastic infantile ganglioglioma, and MRI. Case series that included imaging findings in their reports were included. Imaging studies included head ultrasound and CT and/or MRI scan of the brain. In those reports we reviewed the location of the tumor; its consistency, size, contrast enhancement pattern; and the diffusion characteristics on DWI if these were included.

Results

There were a total of 70 cases of infantile brain tumors treated at BCCH between 1982 and 2012. Of these, 4 cases were coded as GBM and 3 as DIG. Of the 4 patients with GBM, 2 cases were excluded from this study. One was excluded because the infant died shortly after admission to hospital before any radiological studies were performed, with the diagnosis made on postmortem autopsy. The other case was excluded because the tumor's pathological findings "matured" to pleomorphic xanthoastrocytoma on repeat surgery for tumor progression. This case has been reported previously.⁴⁵

TABLE 1. Characteristics of 2 GBM and 3 DIG cases on MRI*

Case No.	MRI Features				Pathological Findings
	Supratentorial Location	Cystic-Solid	ADC Restriction	Enhancement	
1	Yes	Yes	Yes	Heterogeneous (solid)	GBM
2	Yes	Yes	Yes	Heterogeneous (solid)	GBM
3	Yes	Yes	No	Avid (solid)	DIT
4	Yes	Yes	No	Avid (solid)	DIT
5	Yes	Yes	No	Avid (solid)	DIT

* The BCCH experience. Cases 1 and 2 were infantile GBM; Cases 3–5 were DITs.

FIG. 1. Case 1. Admission MR images. **A:** Axial T1-weighted image obtained post-Gd shows the large cystic and solid tumor with associated heterogeneous enhancement of the solid part. **B:** Sagittal T1-weighted image obtained post-Gd showing the extent and size of the cystic component of the tumor. The tumor involves virtually the whole right hemisphere, sparing the frontal region. **C:** Axial T2-weighted image showing the large cystic component of the tumor. The cystic fluid has higher signal than CSF. **D:** An ADC map showing the restricted diffusion of the solid component of the tumor.

The neuroradiological studies of the 2 pathologically proven cases of GBM and the 3 cases of DIG were reviewed. Both cases of GBM were supratentorial, large, involved multiple lobes, had prominent large cystic components, had heterogeneous contrast enhancement, and had a wide area that was adjacent to the overlying dura mater. Both cases demonstrated restricted diffusion of the solid tumoral component on DWI.

In 2 of the 3 DIG cases, the tumors were large, located in the supratentorial compartment, had a large cystic component, and a peripheral solid component that avidly enhanced on contrast studies. The third tumor was predominantly solid with a small cyst. The solid tumor nodule demonstrated avid enhancement on postcontrast imaging in all 3 cases. Also in all 3 cases, the tumor nodule was peripherally located and was adjacent to the overlying dura. There was normal diffusion (i.e., no evidence of restricted diffusion) of the solid part on DWI (Table 1).

The literature review revealed 18 relevant publications on infantile GBM, of which 12 were case reports and 6 were case series.^{5,6,10,12,17,18,21,24–26,28,31,33–36,41,42} From these publications, there were 29 cases of GBM that met our inclusion criteria. The patients underwent either CT scans or MRI based on the patient's age and the clinical presentation. The tumor was located in the supratentorial

FIG. 2. Case 1. Photomicrographs showing histopathological features of specimens obtained at surgery. **A:** Routine H & E staining reveals enlarged, pleomorphic, and hyperchromatic tumor nuclei associated with relatively little fibrillary cytoplasm. Mitoses (arrows) are numerous. **B:** The GFAP staining is strong. **C:** The Ki 67 proliferative index is high. **D:** The reticulin staining is limited to the blood vessel at right. Original magnification $\times 400$ (A), $\times 200$ (B–D). Figure is available in color online only.

space in all cases. It was large in all cases, cystic-solid in 10 cases,^{6,10,12,17,18,24,28,31,32} had heterogeneous enhancement in 9 cases,^{5,12,17,18,21,31,35} Contrast was not mentioned or not given in 19 cases.^{5,6,8,10,12,16,18,24–26,28,34,36,42} Marked enhancement with heterogeneous intratumoral signal due to hemorrhage was reported in 1 case.³³ Two publications included the results of DWI, and both tumors had restricted diffusion in the solid component.^{10,34}

Nineteen reports of desmoplastic tumors were identified and reviewed. From those, 9 publications were single case reports and 10 were case series with a minimum of 2 cases and a maximum of 8 cases. A total of 38 cases were collected. Six cases from 1 publication were excluded because the imaging findings, which were included, did not fit the description by the authors of the radiological find-

FIG. 3. Case 1. Postoperative MRI studies obtained 1 week after diagnosis, biopsy, and decompression of the cyst. **Left:** Axial T2-weighted image showing the progression of the solid component, and recurrence of the cyst. **Right:** Axial T1-weighted post-Gd image showing more avid heterogeneous enhancement of the tumor, as well as subependymal enhancement of the lateral ventricles.

FIG. 4. Admission MRI features in 3 patients (Cases 3–5) with DITs. **A–C:** Case 3. Axial T2-weighted, T1-weighted post-Gd, and ADC map images, respectively, showing cystic-solid tumor, avidly enhancing solid component, and normal diffusibility. **D–F:** Case 4. Axial T2-weighted, T1-weighted post-Gd, and ADC map images, respectively, showing cystic-solid tumor, avidly enhancing solid component, and normal diffusibility. **G–I:** Case 5. Axial T2-weighted, T1-weighted post-Gd, and ADC map images, respectively, showing a predominantly left temporal solid tumor, avidly enhancing, and with normal diffusibility.

ings.²³ The tumor was found to be large and located in the supratentorial compartment in all cases. Cystic-solid consistency of the tumor was either reported by authors or displayed in articles in 28 cases.^{1–4,9,11,14,15,19,20,22,23,27,30,37–40,43,44} A homogeneously and avidly enhancing solid nodule was the most common finding among those cases (27 of 32).^{1,3,4,9,11,14,15,19,22,27,30,38–40,43} Either no contrast was given or the pattern of enhancement was interpreted as heterogeneous in 7 cases.^{2,15,20,23,37,44} Only 1 publication reported the features of DIG on DWI;³⁷ however, the description was vague. The tumor was described as having “hyperintense signal on diffusion weighted images,” but did not describe the imaging pattern on an ADC map because the ADC characteristics were not available for review.³⁷

Examples of a GBM and a DIG from our series are presented below.

Illustrative Cases

Case 1: GBM

A 3-week-old girl born after an uneventful pregnancy and normal vaginal delivery presented with macrocephaly, bulging fontanelle, and increasing irritability. There had been a dramatic increase in the head circumference between birth and 3 weeks. A head ultrasound showed a large heterogeneous lesion centered in the right hemisphere. This lesion consisted of large cyst and a fairly large solid component. Subsequently, a brain MRI study was obtained. This showed a large cystic and solid tumor measuring 10 × 11 × 8 cm that was centered in the right cerebral hemisphere. The cystic component showed homogeneous hyperintense signal on T1- and T2-weighted images. The solid component was hypointense to brain on

T1 and T2 and demonstrated restricted diffusion on the ADC map. The solid component had heterogeneous enhancement (Fig. 1).

A right parietooccipital craniotomy for cyst drainage and tissue diagnosis was done. No attempt was made to resect the tumor because the lesion was very vascular, friable, and necrotic.

Pathological assessment revealed GBM (WHO Grade IV). The tumor cells were disposed in patternless sheets. There was evidence of pseudopalisading necrosis and microvascular proliferation. The Ki 67 proliferative index was high. The tumor cells were negative for IDH1 on immunohistochemical investigation (Fig. 2).

The patient did well postoperatively, and was discharged home. However, she presented 1 week later with a bulging fontanelle, poor feeding, and increasing irritability. Repeat brain MRI showed recurrence of the cyst, blood clot in the cyst, further enlargement of the solid component, and evidence of leptomeningeal dissemination along the lining of the ventricles and along the spinal cord (Fig. 3). Palliative measures were recommended and the child died 1 week later.

Case 3: DIG

A 3-month-old girl presented with increasing head circumference. Her examination confirmed full anterior fontanelle; otherwise she was neurologically intact. Brain MRI showed a large hemispheric intraaxial solid-cystic mass with the solid part centered in the left occipital region. An avidly enhancing tumor nodule was seen. No restricted diffusion was seen on DWI (Fig. 4A–C).

The patient underwent an uneventful left occipital craniotomy and gross-total resection of the tumor. The cystic component was decompressed. The dura overlying tumor was grossly involved.

A DIG was confirmed pathologically. The tumor was composed of short fascicles of spindle cells with oval nuclei and poorly defined cell borders in a collagenous background. The tumor stained positive for glial fibrillary acidic protein (GFAP), synaptophysin, neuron-specific nuclear protein, neurofilament, neuron-specific enolase, and S100. The Ki 67 proliferative index was 10%–11% (Fig. 5).

The patient did well postoperatively, and was discharged home with no complications. On follow-up examination she was found to have a right visual field defect (homonymous hemianopia), but otherwise she was developing well, with no other deficits. Her postoperative MRI studies showed a slight amount of enhancement close to the junction of the sigmoid and left transverse sinus. This was thought to be a small residual lesion. Her MRI studies have shown no recurrence of her disease at 3 years after resection.

Discussion

In this report we outline the MRI features of 2 types of infantile brain tumors, infantile GBM and DIT. These tumors are rare during infancy. Distinguishing between them can be difficult, but it is still important because one tumor is histologically benign and the other is malignant; differentiating these tumors prior to surgery may help

FIG. 5. Case 3. Photomicrographs showing histopathological features of specimens obtained at surgery. **A:** Routine H & E staining reveals spindle tumor cells with thin, wispy, cytoplasmic fibers among thin connective tissue (i.e., reticulin) fibers. **B:** The GFAP staining highlights several spindle tumor cells. **C:** The Ki 67 proliferative index is moderate in this spindle tumor cell area. **D:** The reticulin staining reveals several thin fibers. Original magnification $\times 400$ (A), $\times 200$ (B–D). Figure is available in color online only.

guide treatment, predict surgery-related morbidity, and assist in family counseling. Infantile GBM tumors are usually highly vascular lesions with a potential risk of significant blood loss intraoperatively. Predicting pathological findings preoperatively may help the surgeon plan for only tumor biopsy, chemotherapy, and then second look/resection surgery instead of attempting complete resection, which can be highly morbidity-producing to patients.

Our series showed that both types of tumors appeared large on MRI studies. In the majority of patients, they occupied 1–2 lobes or even the whole hemisphere, were located in the supratentorial space, had a cystic-solid consistency, and had a wide area that was adjacent to the dura. However, GBM tumors had heterogeneous enhancement, and the solid part showed restricted diffusion on MR diffusion studies. On the other hand, the DIG tumors had avid enhancement and did not demonstrate restricted diffusion on the DWI.

Our literature review revealed similar results. However, MR diffusion studies were rarely reported or used to evaluate these lesions. Two reports included diffusion studies of their patients with infantile GBM, and in both of them diffusion was restricted.^{10,34} One report provided a description of the appearance of a DIG tumor on DWI, but interpretation was limited.³⁷

Preoperative DWI provides valuable information about the tumor cellularity and structural integrity by measuring differences in the ADC.²⁹ It is widely used in the assessment of brain tumors, ischemic events, and CNS infections in both adult and pediatric patients. It is easy to perform and requires very little scanning time.

In this report we focused on the diffusion characteristics of 2 common infantile tumors. Other malignant infantile

tile tumors such as PNET are known to have restricted diffusion on DWI, and previous reports have discussed this feature. In 1 report of 12 supratentorial and infratentorial PNETs, all cases showed restricted diffusion on DWI.⁷

Conclusions

We present 2 cases of pathologically proven infantile GBM and 3 cases of DIG. Each group had very suggestive MRI features. The pattern of enhancement and appearance on diffusion studies was very predictive for each group. The information provided by the diffusion studies may be of clinical significance to neurosurgeons. It adds information that may be useful for surgical planning, family counseling preoperatively, and predicting potential intraoperative morbidities.

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Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Steinbok. Administrative/technical/material support: Bader. Study supervision: Steinbok, Bader.

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