

New Frontiers in Pediatric Medulloblastoma

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Case Presentation

B.T. is a 4 year-old boy who was brought by his mother to the emergency department at the local hospital because of headaches over a period of one week. His mother was told by the early childhood education teacher at B.T.'s daycare that her child refused to play games and complained of headaches. B.T. reported episodes of dizziness and he did not like to run around because his legs felt "floppy."

B.T. confirmed the presence of morning headaches when questioned. His mother described three episodes of vomiting in the last 48 hours and increased sleepiness. The emesis was clear fluid or digested food. No fever or diarrhea was associated with the vomiting. Furthermore, there was no history of exposure to uncooked or foreign foods and no recent travel. B.T.'s appetite and activity level had diminished in the week prior to presentation and his mother was unsure about any change in weight. The pre- and peri-natal histories were unremarkable. B.T. had been a healthy child since birth with only occasional colds. His immunizations were up-to-date, he did not have any allergies, and he was not taking any medications.

On physical exam, B.T. sat quietly beside his mother. There were no rashes, bruises, or spinal abnormalities on inspection. His weight and height were in the 80th percentile. Blood pressure and respiratory rate were normal for his age, but the pulse rate was elevated at 120 per minute. The oral temperature was 37.5°C. The cardiopulmonary and abdominal exams were unremarkable. There were no cranial nerve deficits. However, the finger-to-nose test revealed marked dysmetria bilaterally. Bilateral papilledema was evident on fundoscopic examination. B.T. was unable to stand with his eyes closed and demonstrated a wide-based unsteady gait. Muscle bulk in the upper and lower extremities was normal. Tone, power, and reflexes in the upper and lower limbs were normal. There was a flexor plantar reflex bilaterally.

Blood was drawn for complete blood count, creatinine, and electrolytes. The laboratory report showed no CBC abnormality, but B.T. was slightly hypernatremic. A non-contrast CT scan of the head was performed and showed a heterogeneous hyperattenuating mass lesion in the posterior fossa with ventriculomegaly of the third and lateral ventricles. The lesion enhanced homogeneously on contrast CT scan.

The differential diagnosis included medulloblastoma or, less likely, ependymoma or rhabdoid tumour. B.T. was volume resuscitated, admitted to hospital for close observation of neurologic status and vital signs, and started on a corticosteroid. He was transferred to a tertiary paediatric centre where a paediatric neurosurgical and neuro-oncological consultation was obtained for subsequent management. A cranial and spinal MRI was performed with and without contrast. These showed 1) an enhancing infratentorial lesion that filled the fourth ventricle, 2) dilatation of the third and lateral ventricles, and 3) an enhancing nodule at the L3 vertebral level of the spinal canal. Lumbar puncture was not per-

formed due to presence of papilledema and radiologic findings consistent with increased intracranial pressure. An emergent subtotal resection of the cerebellar tumour was performed. Prior to surgery, the family was made aware of the need for post-surgical treatment involving craniospinal radiation and chemotherapy in the event that medulloblastoma was confirmed on pathology. On pathology, a large cell/anaplastic medulloblastoma was observed that stained positive for vimentin and synaptophysin on immunohistochemistry. It was found to have low TrkC expression, ErbB2 positivity in more than 50% of the tumour, and low C-MYC expression levels. After an uneventful postoperative recovery, B.T. received standard-dose craniospinal radiation and boost radiation to the spinal metastasis, as well as chemotherapy. He received concomitant chemotherapy during radiation and post-radiation chemotherapy for eight cycles. Unfortunately, the tumour recurred in the posterior fossa after 12 months. The tumour progressed despite the use of salvage chemotherapy followed by high-dose chemotherapy with bone marrow transplant. B.T.'s family decided to receive follow-up at home and palliative chemotherapy on an outpatient basis. B.T. died peacefully in his sleep two years after his initial diagnosis.

Medulloblastoma: Incidence and Presentation in the Paediatric Population

Medulloblastoma is the second most common paediatric brain tumour and the most common primary tumour of the posterior fossa in children.¹ It represents 20% of childhood intracranial neoplasms and 70-80% of all paediatric embryonal brain tumours. About 80% of medulloblastomas occur in children less than 15 years old with an overall incidence of 0.5 per 100,000 per annum.^{2,3} The median age at diagnosis is nine years and males are affected twice as often as females.⁴ Less than 5% of medulloblastomas are associated with germline mutations. These include tumours arising on the background of Li-Fraumeni (TP53 mutation), Turcot (APC mutation), Gorlin's (PTCH1 mutation), Rubenstein-Taybi, and Coffin-Siris syndromes.⁵ These syndromes harbour mutations that predispose individuals to various cancers in addition to medulloblastoma. Childhood medulloblastomas are typically more aggressive than those found in adults, demonstrating a higher MIB-labelling index and lower apoptotic index.⁶ Medulloblastomas are usually centrally located in the cerebellum, growing into the fourth ventricle. The average symptom duration at presentation is four weeks in children younger than four years and eight weeks for older children.⁷ Obstruction of the CSF outflow tract by the tumour mass can result in hydrocephalus and raised intracranial pressure. These changes are often heralded by headache, lethargy, morning vomiting, bulging of fontanelles in infants, or papilledema. In addition, cerebellar invasion is signaled by the presence of limb or truncal ataxia, dysmetria, intention

tremor, or dysarthria. At diagnosis, 11-43% of medulloblastomas or primitive neuroectodermal tumours are metastatic.⁸ Spread is most common in the neuroaxis. In rare cases, however, patients may develop metastases to bone, lymph nodes, liver, or lungs.⁹

Histology and Molecular Biology

During embryonic development, undifferentiated cells migrate from the proliferating centre of neuroepithelial cells in the posterior tip of the roof of the fourth ventricle to form the granular layer of the cerebellum. Although persistent foci of neuroepithelial cells may be found in the posterior medullary velum,¹⁰ it is not clear if these cells are involved in transformation to malignancy or if tumourigenesis occurs from a different origin. It is hypothesized that medulloblastomas result from transformation of granule cell precursors in the developing cerebellum with pre-neoplastic stages that demonstrate dysregulation of genes controlling cell cycle progression.¹¹ Mutations in several components of the Sonic Hedgehog pathway have been implicated in animal studies as precursors to the development of medulloblastomas.¹² Dysregulation of the Wnt signaling pathway due to sporadic or heritable mutations that result in increased nuclear β -catenin levels is associated with stimulation of the cell cycle in animal medulloblastoma models.¹² Furthermore, upregulation of ErbB2, a receptor tyrosine kinase, can signal cell survival and proliferation through the MAP kinase and AKT cascades.¹³ ErbB2 was demonstrated in 80% of 150 paediatric medulloblastomas, while absent in normal cerebellar tissue.¹³ It is now clear that early events in development and their underlying molecular mechanisms are key in understanding the cause of medulloblastomas.

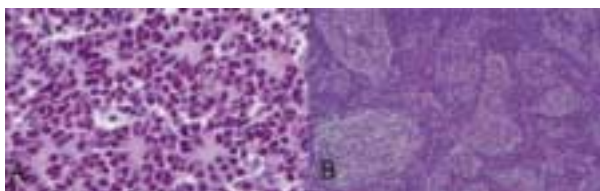


Figure 1. Classic medulloblastoma (A – left). Desmoplastic medulloblastoma (B – right).

Histologically, medulloblastomas are undifferentiated neuroectodermal tumours of the cerebellum, which are classified into six subgroups: classic medulloblastoma, desmoplastic medulloblastoma, medulloblastoma with extensive nodularity, large cell/anaplastic medulloblastoma, melanotic, and medulloblastoma.¹⁴ The classical histology on hematoxylin/eosin staining shows a high density of small cells with blue hyperchromatic nuclei, mitotic figures, and scant cytoplasm.¹⁵ This is the most common subtype found in children, while the desmoplastic variant is common in adults (Figure 1).¹⁶ The desmoplastic variant is characterized by the presence of nodules of tumour cells surrounded by collagen-rich tissue.⁵ Medulloblastoma with extensive nodularity is mostly found in infants and is characterized by extreme nodular desmoplasia with reticulin-free nodules composed of differentiated neurocytic cells interposed among reticulin-rich zones of proliferating cells.¹⁷ Large cell medulloblastomas feature large, pleomorphic nuclei with prominent

nucleoli. Expression of ErbB2 is seen in 40% of large cell anaplastic medulloblastoma.¹⁸ Classic and large-cell medulloblastomas are immunoreactive for vimentin and synaptophysin on immunohistochemistry, while desmoplastic and nodular subtypes are immunoreactive for neuron-specific enolase, synaptophysin, or neurofilaments.¹⁹ Melanotic and medulloblastoma variants are very rare and are recognized by melanin production and variable rhabdomyoblastic differentiation respectively. Although anaplasia is more common in the large cell type, it may also be found in other medulloblastoma types.

Cellular anaplasia has been associated with an increased risk of recurrence or metastasis and poor survival.^{20,21} High mitotic counts, increased vascular surface density, and increased microvessel number have also been proposed as unfavourable prognostic indicators.²² On the other hand, extensive nodularity, which is defined as 96-100% well-circumscribed pale regions of tumour with fibrillar cytoplasm, is associated with a higher probability of survival.^{3,16,23} Recently, an attempt to characterize metastatic medulloblastoma by gene expression analysis revealed over-expression of platelet-derived growth factor receptor alpha, early growth response protein 1, and insulin-like growth factor 2.²⁴ Immunohistochemical analysis of medulloblastoma specimens obtained at surgery has shown value in its ability to provide an extra parameter to predict risk of unfavourable clinical course. Tumours that express trkC or neurotrophin-3 receptor have more favourable outcomes, while those with c-myc or ERBB2 over-expression, chromosome 17p loss (including p53 locus), or anaplastic histology are considered high-risk.^{13,18,25}

The idea that the immunohistochemical profile of individual tumours can predict survival has been formalized by Ray et al. into a model that also incorporates clinical variables. The biological markers with strongest potential to predict survival were p53 (hazard ratio (HR) = 2.29), TrkC (HR = 0.65), and ErbB2 (HR = 1.51) immunopositivity.²⁶ Gene expression profiling has been used to identify markers of survival (e.g. vesicle coat protein b-NAP, PLOD lysyl hydroxylase) and treatment failure (e.g. MYBL2, ribosomal protein genes) in a retrospective data analysis from 55 paediatric patients.²⁷ Use of microarray analysis of tumour gene expression may in the future permit selection of patients with the aim of decreasing the dose of radiation or even avoiding radiation for patients with a favourable gene expression profile.

Diagnostic Principles

Signs and symptoms of increased intracranial pressure and physical exam findings of cerebellar dysfunction should prompt emergent CT and MRI scans of the head. A spinal MRI was also indicated to assess metastatic disease. A medulloblastoma on non-contrast CT imaging classically appears as a well-defined, hyperattenuating, heterogenous, cerebellar mass with surrounding hypodensity consistent with vasogenic edema (Figure 2).²⁸ Atypical features include focal areas of hyperattenuation within the lesion, which may be calcification or hemorrhage, cyst formation, and absence of enhancement on contrast-enhanced imaging. Homogeneous enhancement of the lesion is common on contrast CT. Furthermore, evidence of hydrocephalus on MRI, such as

third and lateral ventricle ventriculomegaly and ependymal transudation, may be present (Figure 3). On MRI, medulloblastomas show greater heterogeneity and appear iso- to hypo-intense relative to white matter on T1-weighted sequences with variable intensity on T2-weighted sequences (Figure 4). Contrast-enhanced T1-weighted images show heterogeneous enhancement of the lesion, with non-enhancing regions representing cystic degeneration or necrosis. MR spectroscopy profile is not specific for medulloblastomas, but typically shows elevated choline peaks, reduced N-acetyl aspartate and creatinine peaks, and sometimes elevated lipid and lactic acid peaks.²⁹



Figure 2. Non-contrast axial CT image of a medulloblastoma.

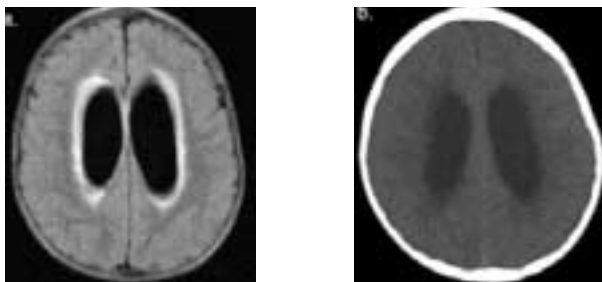


Figure 3. Hydrocephalus on axial MR FLAIR (a) and CT (b) imaging.

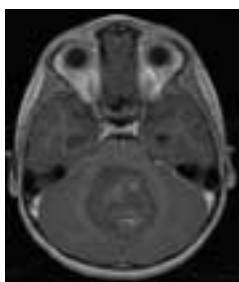


Figure 4. T1-weighted MRI of a medulloblastoma.

Results from CT and MRI are used to stage medulloblastomas according to the Chang system (Table 1), which was originally developed for intra-operative staging.³⁰ Postoperative imaging is used to assess the extent of surgical resection, which has a significant prognostic impact. Surveillance imaging during and after treatment is used to identify recurrence before presentation of clinical symptoms. There has been extensive debate on the role of surveillance imaging in medulloblastoma. However, detection of recurrence by imaging before symptoms recur has been associated with longer survival.³¹

CSF is obtained post-operatively (usually 10 to 14 days after surgery to reduce the chances of false positive results from sloughed cells during surgery) to distinguish M0 from M1 disease by cytological analysis. The use of CSF cytology along with spinal MRI in the initial staging of medulloblastoma increases the sensitivity in detecting leptomeningeal spread.³¹ Lumbar CSF samples are preferred over ventriculo-peritoneal shunt samples because malignant cells are detected at a higher rate in lumbar samples.³²

Treatment

At present, clinical management is based on stratifying patients based on three well-defined prognostic indicators: the patient's age, the extent of residual tumour, and the presence of metastasis.⁸ Patients with average-risk medulloblastoma are older than three years, have no metastases, and have a remnant smaller than 1.5 cm² on postoperative MRI. If these criteria are not met, the patient is classified as high-risk.⁸ While this system has so far been useful for grouping patients in randomized controlled trials, advances in immunohistochemical and genetic profiling of medulloblastomas show promise as future markers of tumour grade and additional determinants of management and prognosis.¹⁸

Patients with newly diagnosed medulloblastoma may be eligible for participation in a clinical trial. Where the option exists, participation in a clinical trial should be discussed with the family. Alternatively, the current non-trial standard treatment approach consists of maximal surgical resection followed by radiation and chemotherapy.³³

Pre-operative decision to biopsy the lesion without attempt at complete surgical resection is mostly considered when patients present with diffuse (disseminated) disease. In most cases, the goal of surgery is maximal tumour resection. Total surgical resection involves careful dissection and evacuation of the tumour from the posterior fossa; however, technical obstacles or risk of extensive neurologic damage may prevent a complete resection. Acute surgical complications following posterior fossa surgery include transient mutism, bulbar palsy, hydrocephalus, aseptic meningitis, hematoma, and air embolism. If mutism occurs, the period of speech loss may last up to one year. Speech returns in the majority of cases, but it rarely normalizes.³⁴ Long-term consequences of posterior fossa tumour resection may include behavioural and attention deficits, addiction problems, uncontrolled temper-tantrums, and phobia.³⁵

The radiation treatment used post-operatively is currently decided on the basis of initial risk stratification and age. Radiation therapy has traditionally consisted of 5,400 to 5,580 cGy to the posterior fossa and approximately 3,600 cGy to the entire neuroaxis. Comparable overall survival rates were seen in a prospective non-randomized trial of patients with non-disseminated disease between 3 and 10 years of age who received adjuvant chemotherapy and either reduced-dose (2,340 cGy) or standard-dose craniospinal radiation.³⁶ This has allowed the use of reduced-dose craniospinal radiation for non-metastatic medulloblastoma patients in the age range for which radiation has been shown to have a substantial impact on intellectual quotient.³⁷ However, a single-centre serial follow-up study showed no difference in academic outcomes such as reading, writing, and math skills in children

treated with reduced-dose versus standard-dose radiation.³⁸ Children who undergo cranial radiation demonstrate a decline in academic ability, social skills, and attention. While quality of life is not significantly affected in long-term survivors, more than 50% suffer severe neuropsychological impairment.³⁹ These findings indicate the need for an organized medical and allied health support system for patients and families that can address cognitive rehabilitation and learning of social skills. Craniospinal radiation therapy is generally avoided in children less than three years old because of intellectual and endocrinological toxicity with conventional doses. Treatment using chemotherapy alone in younger children (usually less than three years old) with non-metastatic disease and gross total tumour resection has been attempted with success.⁴⁰ Alternatively, post-chemotherapy focal radiation is currently offered in phase II studies for infants and young children.⁴¹

T stage

T1	Tumour less than 3 cm in diameter and limited to the classic mid-line position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres
T2	Tumour 3 cm or greater in diameter, further invading one adjacent structure or partially filling the fourth ventricle
T3a	Tumour further invading two adjacent structures or completely filling the fourth ventricle with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing marked internal hydrocephalus
T3b	Tumour arising from the floor of the fourth ventricle or brain stem and filling the 4th ventricle
T4	Tumour further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumour extending to the upper cervical cord

M stage

M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumour cells found in cerebrospinal fluid
M2	Gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M3	Gross nodular seeding in spinal subarachnoid space
M4	Metastasis outside the cerebrospinal axis

Table 1. Chang staging system for medulloblastoma²⁸

Progression-free survival of 85% at three years has been reported with the use of post-operative craniospinal axis radiation and local tumour site boost supplemented by chemotherapy with vincristine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), class=Section3> and cisplatin.⁴² Radiation therapy is started without delay, preferably within 28 days of surgery. When radiation is started, a weekly dose of vincristine is often given. The use of pre-radiation chemotherapy is still a matter of debate, however.⁴³ Recent evidence suggests that adjuvant pre-radiation chemotherapy with reduced-dose radiation in average-risk patients can give a similar five-year recurrence free survival rate as standard radiation and chemotherapy.⁴⁴ In current practice, four to six weeks after completion of radiation therapy, patients are started on a chemotherapy regime (vincristine/CCNU/cis-

platin or other combinations) for 4 to 12 months. Due to the toxicity of cisplatin, patients treated with this agent should undergo a formal audiological exam and renal function monitoring before each cycle of chemotherapy. Hematological toxicity should be assessed by serial CBC at follow up. The clinician should also be vigilant of vincristine-related peripheral neuropathy, which can sometimes present as ileus, weakness, or hyporeflexia.

Recurrent disease may be managed by the use of salvage chemotherapy with agents such as vincristine, cyclophosphamide, carboplatin, lomustine, and etoposide.⁴⁵ Alternatively, high-dose chemotherapy with autologous stem-cell rescue can be considered.⁴⁶ Patients may also be eligible for participation in trials of new therapeutic strategies (Table 2).

Phase II	Cyclophosphamide and surgical resection or radiotherapy followed by Thiotepa, Carboplatin, and autologous peripheral blood stem cell rescue (United Kingdom Children's Cancer Study Group)
Phase I/II	Temozolomide (Duke Comprehensive Cancer Center)
Phase I/II	Lapatinib (Paediatric Brain Tumour Consortium)
Phase II	VNP40101M (Paediatric Brain Tumour Consortium)
Phase II	Antineoplastons A10 and AS2-1 (Burzynski Research Institute)
Phase I	Valproic acid (Children's Oncology Group)
Phase I	Lenalidomide (Paediatric Brain Tumour Consortium)
Phase I	Intrathecal Iodine I-131 monoclonal antibody 8H9 (Memorial Sloan-Kettering Cancer Center)
Phase I	Photodynamic therapy with benzoporphyrin derivative monoacid ring A (Medical College of Wisconsin)

Table 2. Current clinical trials for recurrent medulloblastoma in children.

Prognosis

Without postoperative therapy, the life expectancy from clinical onset is eight to nine months.⁴⁷ Children younger than three years experience progression of the lesion within five years of diagnosis twice as often as older children with a median time to progression of nine months.¹³ Progression-free survival in children with high-risk medulloblastoma is less than 50%⁵ compared to more than 70% in standard-risk medulloblastoma.^{35,44} Metastasis is generally indicative of poor clinical outcome. Some evidence suggests that the period of recurrence risk following successful treatment may be calculated by Collin's law, which states that the highest risk of recurrence is in the number of months after treatment equalling the age of the child plus nine months.^{48,49} Nevertheless, recurrence has been observed after very long periods of clinical remission. Most recurrences occur within the first two years after initial treatment, which may justify surveillance imaging during this period. When a radiation dose greater than 50 Gy is given to the posterior fossa volume, the most common site for recurrence is outside the posterior fossa.⁵⁰ Relapse in children previously treated with craniospinal radiation carries a five-year survival of less than 10%.⁵¹

Psychosocial Considerations

In order to ensure the psychosocial well-being of patients facing frequent hospital visits for imaging, chemotherapy, radiation therapy, and follow-up, the clinician must be aware of signs of depression, anxiety, and failure to cope with daily activities such as eating, school, and play. He or she must also develop an understanding of the family values, beliefs, and stresses. This is best accomplished by providing care in a multidisciplinary team consisting of the integration of resources from nursing, social work, child psychology, psychiatry, physical therapy, and occupational therapy. In the case of treatment failure, access to and coordination with specialized child palliative care services is essential.⁵² Careful explanation of the role of the palliative care team and ongoing support from the primary care provider are important components in providing parents with a sense of control over end-of-life decisions for their child. Furthermore, while the child is still neurologically stable, efforts should be made to encourage activities through organizations such as the Make a Wish Foundation and summer camps for children with brain tumours.

Conclusions

Our growing understanding of the molecular features of medulloblastomas has enabled recent efforts to characterize tumours on a molecular level in order to inform treatment strategies. While survival rates have improved significantly in the past 30 years due to reduced perioperative mortality and improved radiation and chemotherapeutic strategies, we have also begun to appreciate the negative impact of radiation therapy. The advent of novel biological therapies and improved risk stratification to guide therapy will hopefully lead to improved survival with reduced sequelae of treatment. Despite the advances in diagnosis and treatment, medulloblastomas in children carry significant morbidity and mortality. Efforts should be made to follow patients within the structure of an interdisciplinary team that can monitor the psychological well-being of the patient, provide parent education, and provide resources for rehabilitation, school reintegration, as well as palliative and respite care.

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