Ganglioglioma Arising From Desmoplastic Medulloblastoma: A Case Report and Review of Literature

Santosh Valvi, MBBS, MD, FRACP,[a] David S. Ziegler, MBBS, BSc (Med), FRACP, MD, PhD[b,c]

We describe a case of medulloblastoma maturating into ganglioglioma during therapy. A 10-month-old boy was diagnosed with a desmoplastic medulloblastoma and was treated with gross total resection followed by induction chemotherapy. A recurrence in the tumor bed during therapy was managed with focal radiation therapy and consolidation chemotherapy. After further progression, the recurrent tumor was resected completely. The histopathology revealed a benign ganglioglioma with no residual medulloblastoma. This case raises the possibility that a malignant medulloblastoma can differentiate into a benign tumor and suggests that differentiation therapy may have value in the treatment of medulloblastoma.

Medulloblastoma, an embryonal tumor of the cerebellum, is the most common childhood malignant brain tumor.[1] The current World Health Organization classification describes a classic form with 4 distinct variants: desmoplastic, medulloblastoma with extensive nodularity (MBEN), anaplastic, and large-cell forms.[2] More recently it has also been stratified into 4 major molecular subgroups with different clinical outcomes for each group.[3] Desmoplastic tumors fall into the Sonic Hedgehog (SHH) pathway group and are more common in infants and adults. Infants with desmoplastic tumors have an excellent prognosis, suggesting a unique biology.[4]

We encountered a patient with a desmoplastic medulloblastoma, revealing complete maturation to adult ganglion cells during therapy. There have been a very small number of previous case reports of either focal transformation of medulloblastoma into mature neuronal tumors, or complete maturation into a benign tumor.

CASE REPORT

A previously well 10-month-old boy presented with a 6-week history of intermittent fever, irritability, and loss of developmental milestones. Clinical examination was significant for generalized hypertonia, hyperreflexia, and right upper limb dysmetria. Neuroimaging in the form of ultrasound and MRI of the brain revealed the presence of a large posterior fossa mass with accompanying hydrocephalus. An ophthalmologic review revealed the presence of bilateral papilledema. There was no history of cancer in other family members.

He proceeded to have an external ventricular drain inserted followed by a limited resection of the mass as he was too unwell at presentation for a more definitive procedure. After improvement in his clinical condition, second look surgery was performed 3 weeks later and gross total resection was achieved. A small metastatic nodule was found on the surface of the cerebellum and was resected. Histopathology revealed

[a]*Princess Margaret Hospital for Children, Perth, Western Australia, Australia;* [b]*Kids Cancer Centre, Sydney Children's Hospital, Randwick, New South Wales, Australia; and* [c]*School of Women's and Children's Health, University of New South Wales, Australia*

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Address correspondence to Santosh Valvi, MBBS, MD, FRACP, Department of Pediatric and Adolescent Clinical Hematology and Oncology and Blood and Marrow Transplantation, Princess Margaret Hospital for Children, Roberts Rd, Subiaco WA, Australia 6008. E-mail: santosh.valvi@health.wa.gov.au

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a desmoplastic medulloblastoma (Fig 1). Immunohistochemistry revealed positive staining for YAP/GAD, cytoplasmic β-catenin (with no nuclear staining), low level N-MYC gain (ratio 1.8:1), and wild-type for TP53. BRAF V600E was negative. The Illumina HumanMethylation 450K array and Nanostring Gene expression profiling confirmed that the initial tumor was SHH pathway medulloblastoma. The O6-methylguanine-DNA methyltransferase promoter was not methylated, and there were no chromosomal abnormalities. Germline testing did not reveal any underlying suppressor of fused homolog mutations.

He was treated as per the Children's Oncology Group protocol ACNS0334,[5] with a plan for 3 cycles of induction chemotherapy followed by 3 cycles of consolidation chemotherapy with stem cell support. An MRI repeated after 3 cycles of induction chemotherapy revealed tumor recurrence with a discreet nodule in the tumor bed (Fig 2). The surgical attempt at resection was unsuccessful but a biopsy revealed some viable tumor cells. In view of this disease recurrence, he received focal stereotactic radiation therapy (RT) at a dose of 4500 rads. The next MRI after RT had some features suggestive of further tumor progression, but postradiation flair was considered in the differential. He proceeded to have 1 cycle of consolidation chemotherapy with thiotepa and carboplatin followed by stem cell rescue. A repeat MRI after this revealed persistence of the enlarged nodule. A further resection was successfully achieved, with complete resection of a calcified, well circumscribed nodule. Histopathology revealed a well differentiated ganglioglioma with no evidence of medulloblastoma (Fig 3). The Illumina HumanMethylation 450K array confirmed a methylation pattern consistent with

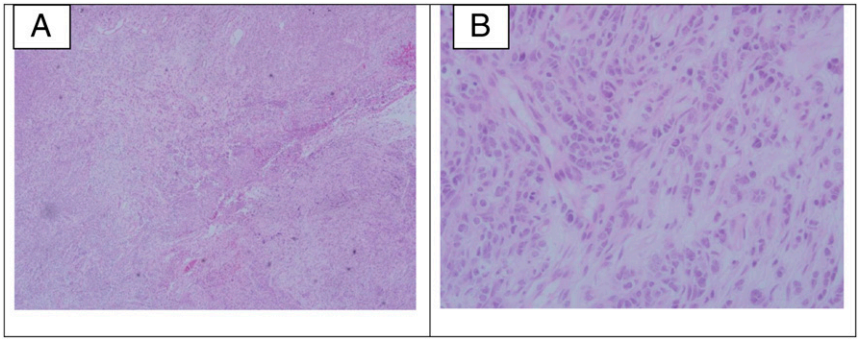

FIGURE 1
Hematoxylin and eosin stain of tumor at diagnosis. A, 4× magnification and B, 400× magnification revealing a highly cellular small blue cell tumor. The cells had small round to oval nuclei with mild to moderate hyperchromasia and minimal cytoplasm.

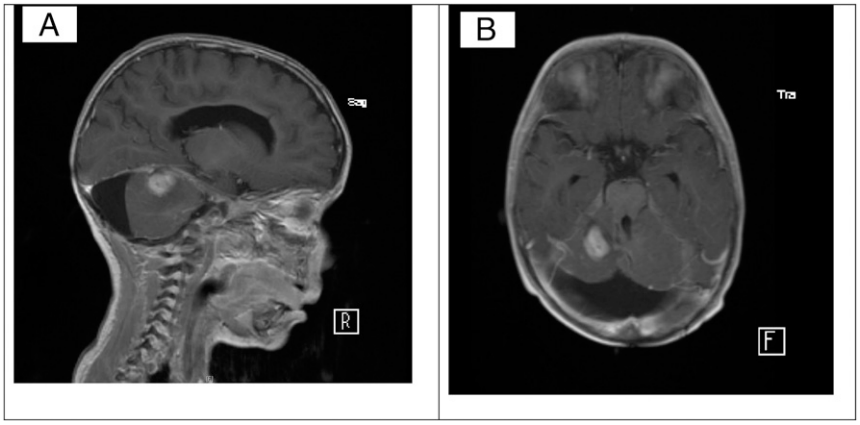

FIGURE 2
MRI scan at recurrence. A, Sagittal and B, axial MRIs at relapse, revealing a discrete enhancing nodule in the tumor bed.

ganglioglioma, with no correlative features with the original SHH medulloblastoma. BRAF mutation testing revealed no evidence of V600E mutation or BRAF fusions. He completed his consolidation chemotherapy without any further complications and remains alive and well 6 years since his original diagnosis.

DISCUSSION

Medulloblastoma, the most common malignant brain tumor of childhood,[1] is a heterogeneous disease and histologically described as a classic form with 4 variants.[6] More recently, it has been classified molecularly into 4 subgroups.[3] With advances in the multimodal therapy, the prognosis has significantly improved for the majority of the patients.[1] Gangliogliomas are rare, World Health Organization Grade 1 ganglion cell tumors with a mixture of mature neurons and glial cells, as well as a neoplastic glial component.[7,8] The prognosis is good with only surgical intervention necessary in most cases.[9,10]

Extensive posttherapeutic neuronal maturation, which is commonly encountered in peripheral neuroblastoma,[11] is rarely seen in medulloblastoma. There have been 5 previous case reports of differentiation of medulloblastoma into mature neural or glial components after treatment (Table 1).

TABLE 1 Case Reports of Medulloblastoma Differentiating Into a Benign Tumor

	Age at Diagnosis	Pathology at Diagnosis	Treatment at Diagnosis	Age at Relapse	Pathology at Relapse	Outcome
Cai et al[11]	3 mo	Desmoplastic medulloblastoma	Surgery Chemotherapy	11 mo	Exclusive gangliocytoma	Died at 28 mo
Cai et al[11]	3 y	Medulloblastoma	Surgery RT Chemotherapy	11 y	Extensive gangliocytoma	Alive
Chelliah et al[14]	22 mo	MBEN	Surgery Chemotherapy	28 mo	Gangliocytoma	Alive
Kudo et al[12]	15 y	Medulloblastoma	Subtotal resection RT Chemotherapy	17 y	Medulloblastoma with focal ganglioglioma	Died at 19 y
Kubota et al[13]	8 y	Medulloblastoma	Surgery Chemotherapy RT	8 y	Medulloblastoma Focal gangliocytoma	Alive at 10 y
Bernert et al[15]	2 wk	MBEN	Surgery	6 mo	Nodular lesion in posterior fossa	Not discussed in the article
		Ganglioglioma Both MBEN and gangliоglial differentiation were seen in the tumor at the time of diagnosis without any previous therapy	Chemotherapy		Peri-medullary enhancement, especially in the cauda equine region	

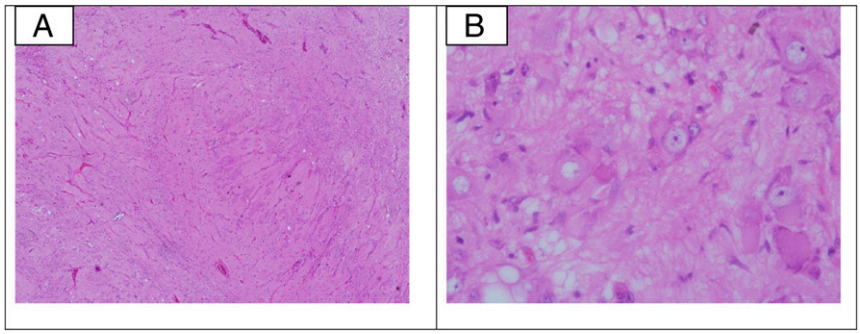

FIGURE 3
Hematoxylin and eosin stain of tumor at recurrence. A, 4× magnification and B, 400× magnification, revealing reduced cellularity and large mature-appearing ganglion cells with variable dysmorphic features, including clumped Nissl substance and occasional binucleate neurons. There is evidence of dead tumor with dystrophic calcification suggesting the possibility of treatment effect. There are no primitive elements seen.

This maturation can be either focal as described by Kudo et al[12] or Kubota et al[13] or near complete as in the cases reported by Cai et al[11] or Chelliah et al.[14] Spontaneous maturation of medulloblastoma into ganglioglioma at diagnosis has also been reported.[15] Notably, 3 of these cases described tumors that were desmoplastic (or MBEN), whereas histology was unclear in the remaining 3.

In the case reported here, the initial tumor also revealed the classic histologic features of desmoplastic medulloblastoma. After chemotherapy and RT, no medulloblastoma cells were identified in the recurrent mass lesion. Instead, mature ganglion cells in the form of ganglioglioma were seen. Given the time course, and the location of the second tumor, it is most likely the ganglioglioma was not a primary tumor, rather, the original medulloblastoma remnants differentiated into the mature cells. It is possible that chemotherapy and RT triggered this process although spontaneous maturation cannot be excluded.

Granule neuron precursor cell is the candidate cell of origin for desmoplastic medulloblastoma in young children.[16] Secondary to certain biological factors, like persistent SHH stimulation, granule neuron precursor cells fail to differentiate and develop into medulloblastoma. As this case demonstrates, and other case reports have shown, medulloblastoma cells may have a potential for differentiation into more mature cells like neurons and glia.[14] This provides a rationale for employing differentiation therapy as a novel therapeutic strategy to attempt to transform the highly malignant medulloblastoma cells into more mature and benign cells. Retinoic acids are used for this purpose in the treatment of neuroblastoma. Similarly, their activity is currently being investigated in an ongoing clinical trial in medulloblastoma.

Young age at diagnosis is a recognized adverse prognostic factor for medulloblastoma, principally because of the inability to use craniospinal RT in young infants.[17,18] However, the prognosis is modified by other factors including the histologic and molecular

subtypes, the presence or absence of metastatic disease, and the degree of residual tumor. Infants with SHH pathway tumors and desmoplastic histology have a far better prognosis compared with older children. Even without RT, young children with desmoplastic medulloblastoma tend to have a good outcome.[19–21] There are also suggestions that RT may be successfully delayed in patients with desmoplastic subtypes.[22] A meta-analysis confirmed desmoplastic histology as an independent favorable prognostic factor prompting the authors to suggest controlled deescalation of treatment.[23] It is unclear whether focal RT to the tumor bed is of benefit for these children; however, the majority are cured even with the omission of craniospinal RT.[20] The maturation of medulloblastoma into a benign lesion at a younger age, as seen in our patient, as well as in the reported cases in the literature, may also suggest unique biological characteristics at this age, as is true in the case of neuroblastoma.

Currently, disease recurrence after therapy for medulloblastoma that includes high dose chemotherapy and RT has a very poor prognosis. For this reason, our patient was also almost considered incurable and would have been offered palliative therapy, but the biopsy was instrumental in proving the benign nature of the underlying pathology. This highlights the importance of considering a biopsy in the event of recurrent to disease to allow for histopathological examination of confirmation of the underlying pathology.

CONCLUSIONS

We have reported a case of an infantile desmoplastic medulloblastoma maturing completely into a ganglioglioma during therapy with a subsequent survival of more than 6 years. Desmoplastic medulloblastoma is more common in children younger than 3 years of age and has a better prognosis.[14] As in neuroblastoma, maturation of medulloblastoma cells may be associated with a better prognosis.[11] This case suggests that some types of medulloblastoma may have more potential for maturation, and research to identify the pathways that induce differentiation may facilitate the development of novel therapeutic approaches.

ABBREVIATIONS

MBEN: medulloblastoma with extensive nodularity
RT: radiation therapy
SHH: Sonic hedgehog

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