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CASE REPORT

Recurrent Wnt medulloblastoma treated with marrow-ablative chemotherapy and autologous hematopoietic progenitor cell rescue: a dual case report and review of the literature

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Abstract

Wnt-activated medulloblastoma (MB) confers an excellent prognosis. However, specific treatment strategies for patients with relapsed Wnt-MB are unknown. We report two patients with recurrent beta-catenin nucleopositive Wnt-MB successfully treated by incorporating marrow-ablative chemotherapy and autologous hematopoietic progenitor cell rescue (HDCx/AuHPCR). We also present a review of the literature for previously reported cases of relapsed Wnt-MB. We propose that patients with recurrent Wnt-MB may be treated using a multi-disciplinary approach that includes HDCx/AuHPCR with or without re-irradiation.

Keywords Recurrent · Medulloblastoma · Wnt · CTNNB1 · Marrow-ablative chemotherapy · Case report

Introduction

Medulloblastoma (MB) is the most common malignant brain tumor of childhood [1]. Current molecular stratification has identified four subgroups: Wingless pathway (Wnt), Sonic Hedgehog Homolog, group 3, and group 4 [2]. Wnt-MB is the rarest subgroup and patients have an excellent prognosis with > 95% surviving beyond 5 years [2, 3]. Relapse is quite uncommon; Ramaswamy et al. reported that only three (1.5%) of 203 relapsed MB were of the Wnt subgroup [4], whereas the risk of MB relapse across all subgroups is 20–30% [5, 6]. Due to their rarity, specific treatment strategies for patients with relapsed Wnt-MB are not clear. Herein, we present two patients with recurrent Wnt-MB treated with strategies incorporating marrow-ablative high-dose chemotherapy (HDCx) followed by autologous hematopoietic progenitor cell rescue (AuHPCR). Moreover, we provide a focused review of the literature for patients with relapsed Wnt-MB.

Methods

A retrospective chart review identified patients treated at Nationwide Children's Hospital. A detailed English-language literature search without date restrictions was performed using PubMed/MEDLINE.

Results

Case one

An eight-year-old female presented with a 2-week history of progressive headaches, somnolence, and unsteady gait. Brain magnetic resonance imaging (MRI) demonstrated a T1-

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isointense mass (3.3 × 3.9 × 4.0 cm) with enhancement and restriction on diffusion-weighted imaging (DWI), located centrally in the vermis (Fig. 1a and b). Spine MRI and lumbar cerebrospinal fluid (CSF) cytology were negative for tumor. Gross total resection (GTR) of the mass was achieved. The pathology was classic Wnt-MB. The tumor was immunopositive for nuclear beta-catenin, YAP-1, and synaptophysin, while immunonegative for GAB-1. Next-generation sequencing revealed *CTNNB1* mutations and DNA methylation clustering consistent with classic Wnt-MB. Monosomy-6 was negative on fluorescence in situ hybridization (FISH) and 10–15% of cells displayed divergent melanocytic and rhabdomyoblastic markers on immunohistochemistry (IHC) staining. The patient received 18 Gy craniospinal irradiation (CSI) with primary site boost to 54 Gy, concomitantly with weekly vincristine, followed by a maintenance regimen of nine alternating cycles of vincristine/etoposide, vincristine/carboplatin, and vincristine/cyclophosphamide [7]. Ten months after completion of therapy, surveillance brain MRI demonstrated an enhancing 14 × 10 × 12 mm nodule with restricted diffusion along the operative bed (Fig. 1c and d). Spine MRI and lumbar CSF cytology were negative for tumor. Histopathology of the recurrent tumor was similar to that of the original tumor, except the recurrent tumor was negative for melanocytic and rhabdomyoblastic markers. After GTR of the mass was achieved, three cycles of HDCx/AuHPCR with carboplatin (510 mg/m^2) and thiotepa (300 mg/m^2) were administered. She is now disease-free for 48 months following end of therapy.

Case two

A 17-year-old male presented with signs of increased intracranial pressure. Brain MRI demonstrated an enhancing fourth ventricular mass (5.0 × 3.5 × 4.0 cm) causing tonsillar herniation and obstructive hydrocephalus (Fig. 2a and b). Spine MRI and lumbar CSF cytology were negative for tumor. GTR of the mass was achieved and pathology confirmed classic Wnt-MB. Tumor cells were immunopositive for nuclear beta-catenin and YAP-1 while immunonegative for GAB-1; in this case, the presence of monosomy-6 was detected by FISH. As per ACNS0331 [8], the patient received 23.4 Gy CSI with posterior fossa boost to 54 Gy, accompanied by

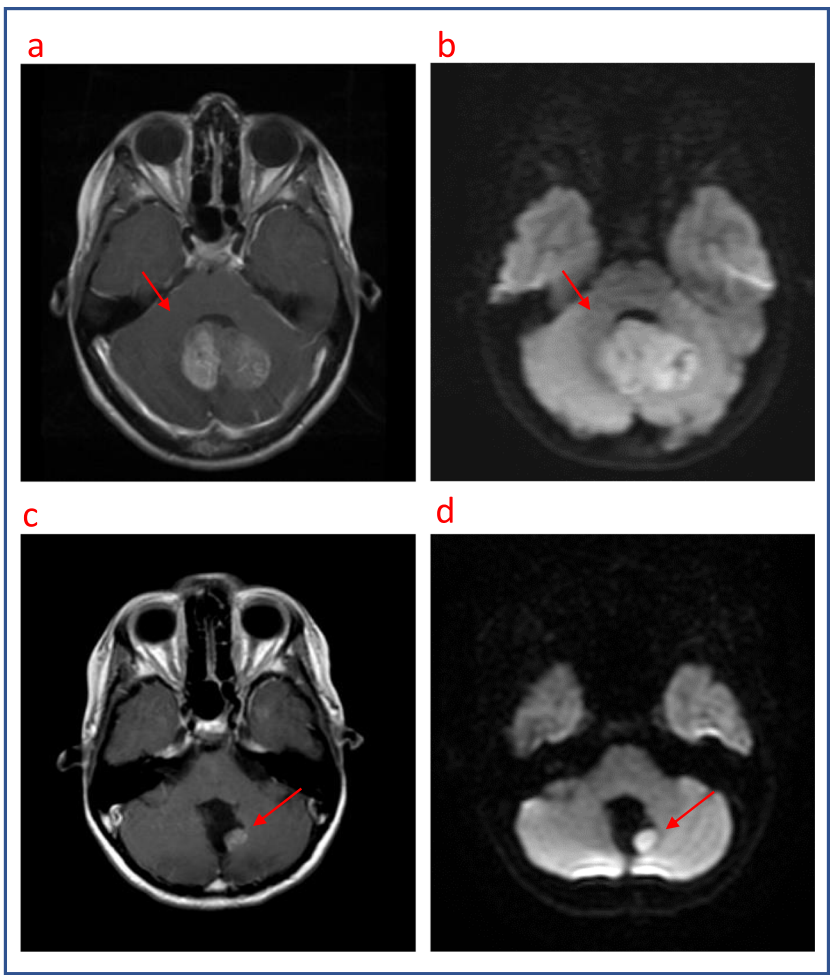

Fig. 1 Patient one magnetic resonance imaging (MRI) at initial diagnosis: **a** axial diffusion-weighted imaging (DWI) and **b** T1-weighted imaging (T1WI) demonstrate an enhancing tumor located in the central vermis. MRI at relapse: **c** axial DWI and **d** T1WI demonstrate an enhancing nodule within the surgical resection cavity. Red arrows indicate the lesion

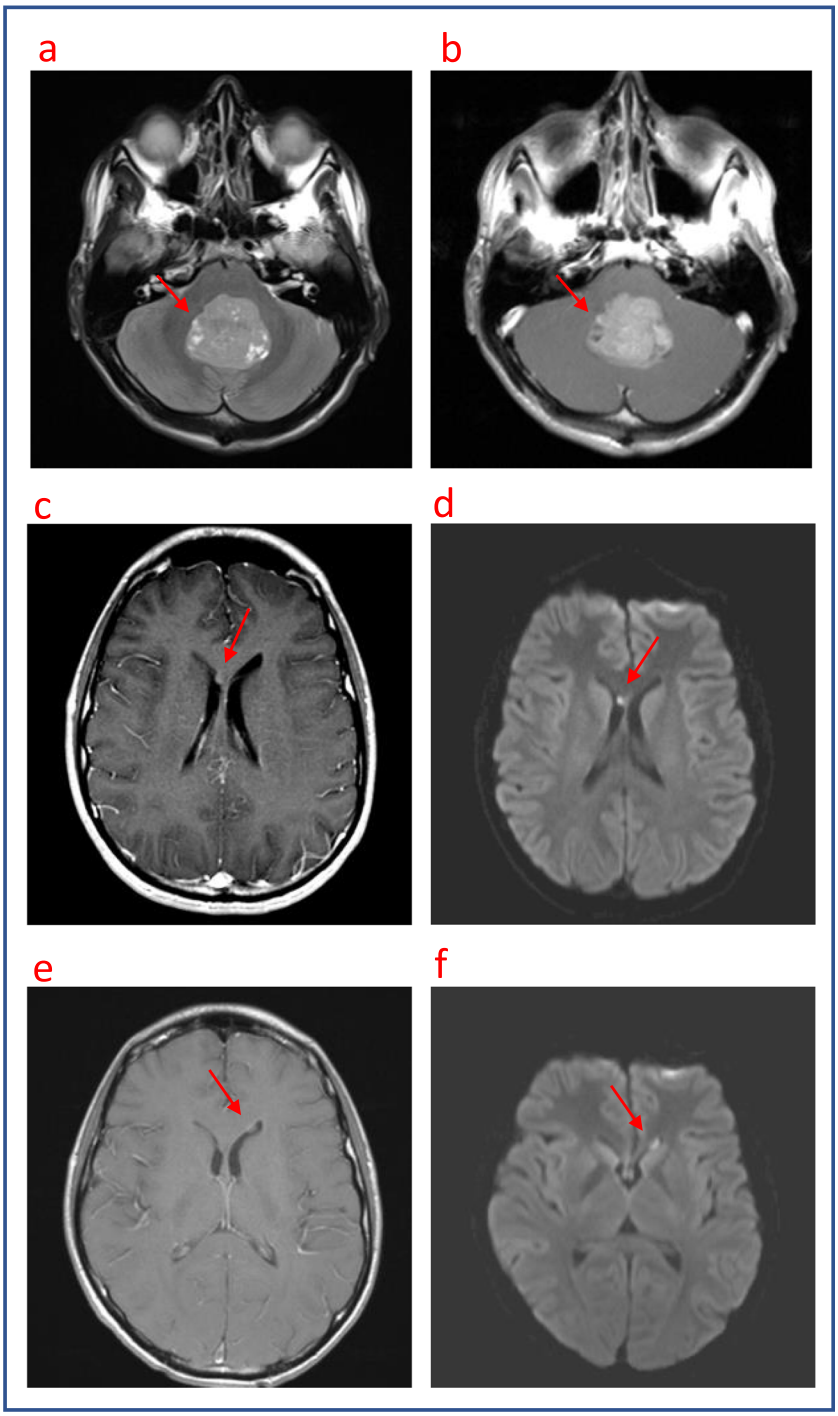

Fig. 2 Patient two magnetic resonance imaging (MRI) at initial diagnosis: **a** axial T2-weighted imaging (T2WI) and **b** T1-weighted imaging (T1WI) demonstrate an enhancing tumor in the fourth ventricle. MRI at first relapse: **c** axial diffusion-weighted imaging (DWI) and **d** T1WI demonstrate a nodule within the right frontal horn. MRI at second relapse: **e** axial DWI and **f** post-contrast T1WI demonstrate a nodule in the left frontal horn. Red arrows indicate the lesion

concomitant weekly vincristine, followed by nine cycles of lomustine/cisplatin/vincristine alternating with cyclophosphamide/vincristine. Fifteen months following completion of therapy, a focus of enhancement in the right lateral ventricle was noted on brain MRI (Fig. 2c and d). The patient received salvage therapy consisting of temozolomide, irinotecan, and bevacizumab as per ACNS0821 [9], followed by 20 Gy stereotactic radiosurgery at the site of recurrence. A second metastatic relapse occurred 11 months after radiosurgery where a focus of hyperintense tissue on DWI with decreased intensity on apparent diffusion coefficient was noted in the left lateral ventricle (Fig. 2e and f). A biopsy was performed and pathology confirmed classic Wnt-MB, immunopositive for nuclear beta-catenin and YAP-1, immunonegative for GAB-1, and again positive for monosomy-6 by FISH. Treatment was initiated with two induction cycles of etoposide/cyclophosphamide, followed by two cycles of HDCx/AuHPCR with carboplatin (500 mg/m^2) and thiotepa (500 mg), and

Table 1 Cases of Wnt-MB reported in the literature and in the present study*

Reference	Patient no.	Histology	Relapse site		Relapse treatment		Follow-up after 1st relapse (months)	Status
			R1	R2 (R3)	R1	R2 (R3)		
Ramaswamy et al., 2013 [4].	1	Classic	Unspecified**	Unknown	RT	HDCx with AuHPCR + TMZ/etoposide	102	Alive
Ramaswamy et al., 2013 [4].	2	Classic	Unspecified**	n/a	Unknown	n/a	65	Alive
Ramaswamy et al., 2013 [4].	3	Classic	Unspecified**	n/a	Unknown	n/a	8	DOD
Sabel et al., 2016 [10].	4	Classic	Posterior fossa	Unknown	HDCx (carboplatin/etoposide) with AuHPCR	TMZ/cyclophosphamide (IT) (R3: HITSKK-92, Mtx/cytarabine)	42	DOD
Sabel et al., 2016 [10].	5	Classic	Supratentorial (Met)	Unknowns	No treatment	No treatment (R3: TMZ/etoposide/GEMOX)	45	AWT
Sabel et al., 2016 [10].	6	Classic	Spinal (Met)	Unknown	TMZ	TMZ	17	DOD
Sabel et al., 2016 [10].	7	Classic	CSF (Met) and spinal (Met)	Unknown	Surgery + etoposide (IT) + RT (focal)	TMZ	16	DOD
Sabel et al., 2016 [10].	8	Desmoplastic	Posterior fossa and unknown site (Met)	n/a	Etoposide (oral)	n/a	2	DOD
Sabel et al., 2016 [10].	9	Classic	Spinal (Met)	Unknown	Trophosphamide/etoposide + RT (focal)	TMZ/etoposide (IT)	29	DOD
Sabel et al., 2016 [10].	10	Classic	Posterior fossa	n/a	Surgery + HDCx (TT/etoposide) with AuHPCR + carboplatin/etoposide	n/a	18	DOD
Sabel et al., 2016 [10].	11	Classic	Posterior fossa and CSF (Met)	n/a	Unknown	n/a	29	DOD
Tsang et al., 2019 [11].	12	Unknown	Supratentorial (Met)	n/a	HDCx with AuHPCR + RT (focal)	n/a	154	Alive
Narayan et al., 2019 [12].	13	Unknown	Primary site	n/a	Unknown	n/a	Unknown	Unknown
Narayan et al., 2019 [12].	14	Unknown	Leptomeningeal (Met)	n/a	Unknown	n/a	Unknown	Unknown
Narayan et al., 2019 [12].	15	Unknown	Supratentorial (Met)	n/a	Unknown	n/a	Unknown	Unknown
Korshunov et al., 2019 [13].	16	Classic	Lateral ventricles (Met)	n/a	RT + chemotherapy	n/a	48	Alive
Korshunov et al., 2019 [13].	17	Classic	Spinal (Met)	n/a	Chemotherapy	n/a	78	Alive
Bezerra Salomão et al., 2018 [14].	18	Unknown	Unknown	n/a	Unknown	n/a	Unknown	DOD
Bezerra Salomão et al., 2018	19	Unknown	Unknown	n/a	Unknown	n/a	Unknown	DOD

Table 1 (continued)

Reference	Patient no.	Histology	Relapse site		Relapse treatment		Follow-up after 1st relapse (months)	Status
			R1	R2 (R3)	R1	R2 (R3)		
[14].								
Bezerra Salomão et al., 2018 [14].	20	Unknown	Unknown	n/a	Unknown	n/a	Unknown	DOD
Bezerra Salomão et al., 2018 [14].	21	Unknown	Unknown	n/a	Unknown	n/a	Unknown	DOD
Present case one	22	Classic	Primary site	n/a	Surgery + HDCx (carboplatin/TT) with AuHPCR	n/a	44	Alive
Present case two	23	Classic	Right lateral ventricle (Met)	Left lateral ventricle (Met)	TMZ/irinotecan/bevacizumab + stereotactic radiosurgery	Cyclophosphamide/etoposide (oral) + HDCx (carboplatin/TT) with AuHPCR	33	Alive

R1 first relapse, *R2* second relapse, *R3* third relapse, *DOD* dead of disease, *AWT* alive with tumor, *Met* metastatic relapse, *NS* not specified, *n/a* not applicable, *RT* radiotherapy, *IT* intrathecal, *TMZ* temozolomide, *Mtx* methotrexate, *TT* thiotepa, *HDCx* high-dose chemotherapy, *AuHPCR* autologous hematopoietic progenitor cell rescue, *GEMOX* gemcitabine + oxaliplatin. HITSKK-92: surgery followed by three cycles of intravenous chemotherapy (cyclophosphamide/vincristine/methotrexate/carboplatin/etoposide) plus intraventricular methotrexate [1]

*A literature search was performed using PubMed/MEDLINE to identify previous reports of patients with relapsed Wnt-MB using the following search query: ((“medulloblastoma”[MeSH Terms]) AND (wnt OR wingless)) AND ((relapsed OR recurrent OR relapse OR recurrence)). The search was limited to English-language articles and did not have date restrictions

**Ramaswamy et al. reported one local and two metastatic relapses, but patients were not specified

reduced-dose CSI (18 Gy) with a relapse site boost to 54 Gy. He is now disease-free 7 months following completion of therapy. Longer follow-up is needed to monitor for recurrence.

Literature review

Twenty-one patients with relapsed Wnt-MB from six publications were identified and are summarized in Table 1 [4, 10–15]. Because all cases were reported in the context of larger cohort studies, not all metrics of interest were reported. Survival data were reported for 14 patients and treatment regimens were not reported for all patients. Of 369 relapsed MB cases reported within the six publications, 5.7% (21/369) were of the Wnt subgroup. Of the 14 patients with survival data, six patients were reported alive (one alive with tumor) with a median follow-up of 82 months after first relapse (range, 33 to 154 months). All patients received RT as part of their primary therapy. At first relapse (R1), four patients (19%) experienced local relapse, 11 (52%) experienced metastatic relapse, two (10%) experienced multifocal relapse, and relapse site was unreported in four (19%). Six patients experienced a second relapse (R2) and two relapsed a third time (R3). Two patients at R1 and one at R3 underwent surgical resection. Six patients received radiotherapy (RT) at R1, with one receiving RT only. RT field was local for three patients, unspecified for three patients, and one patient received stereotactic radiosurgery at the site of recurrence. No patient received RT at R2 or R3. Nine patients at R1, five at R2, and two at R3 received chemotherapy.

Discussion

Relapsed MB generally confers a poor prognosis across all subgroups — in a retrospective analysis of 173 patients with relapsed MB, Johnston et al. reported 23 (11.4%) alive at the time of survey with overall survivals (OS) of 16.9% at 3 years and 12.4% at 5 years [16]. Our literature search (Table 1) revealed that the 3-year OS for patients with relapsed Wnt-MB was 56.3% (95% CI: 29.6–76.3%) (Fig. 3). The two longest event-free survivors (patients 1 and 12) received HDCx/AuHPCR with reduced RT as part of relapse treatment. Moreover, re-irradiation was avoided in the third event-free survivor (patient 17). Overall, of those whose treatment regimens were reported, five patients (46%) were re-irradiated at relapse. In the present report, patients one and two received RT following HDCx. This is similar to the Head Start I and II clinical trials, in which patients with supratentorial primitive neuroectodermal tumors received RT following HDCx if they were > 6 years old at diagnosis and/or had residual disease after induction.

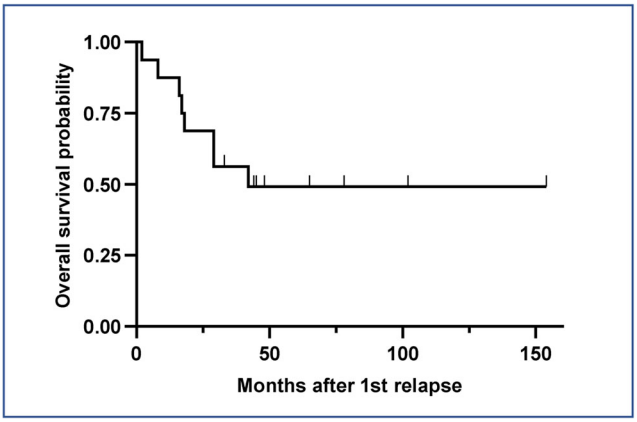

Fig. 3 Kaplan-Meier curve for overall survival of patients with adequate follow-up information. Vertical tick marks indicate censoring. The overall survival at 3 years following 1st relapse was 56.3% (95% CI: 29.6–76.3%)

In order to minimize RT, HDCx/AuHPCR has been incorporated into the treatment of high-risk and relapsed MB [17–19]. In a cohort of 25 patients with recurrent MB treated by high-dose carboplatin/thiotepa/etoposide, Dunkel et al. reported six event-free survivors (median follow-up of 151.2 months); re-irradiation was spared in three survivors [20]. Similarly, a report from the Mayo clinic showed that out of 10 adult patients with recurrent CNS embryonal tumors (eight MB and two primary cerebral/CNS neuroblastoma) treated with thiotepa-based HDCx without re-irradiation, five patients (50%) remained alive after 2.9 years [21]. Importantly, the use of RT at initial diagnosis may impact the efficacy of HDCx at relapse. In a study by Gururangan et al., previously irradiated ($n = 12$) and non-irradiated ($n = 7$) patients with relapsed Wnt-MB were treated with HDCx-based regimens; all 12 patients who had received RT prior to recurrence died (median 35 months), while there were three long-term survivors in the group that had not been irradiated [22].

Other studies have shown less encouraging results. In an analysis of the HIT-SIOP-PNET4 trial for standard-risk MB, Sabel et al. reported that incorporation of HDCx (one thiotepa/etoposide; two carboplatin/etoposide; 12 unspecified) was not associated with prolonged survival in 15 relapsed patients [10]. Similarly, Bode et al. described that HDCx (carboplatin/etoposide/thiotepa) did not benefit patients with recurrent primitive neuroectodermal tumors on the HITREZ-97 German national trial [23]. Gajjar et al. proposed five indicators of responsiveness: (1) minimal residual disease at the time of AuHPCR, (2) local recurrence, (3) chemotherapy-responsive disease, (4) use of RT after HDCx, and (5) minimal therapy at diagnosis [24].

Based on our experience, we suggest that a subset of patients with recurrent Wnt-MB may be treated utilizing an approach that incorporates HDCx/AuHPCR. To evaluate the benefits of reduced re-irradiation in our patients as well as

monitor for recurrence, longer follow-up is needed. Prospective studies evaluating treatment strategies in patients with relapsed Wnt-MB are warranted.

Abbreviations MB, Medulloblastoma; Wnt, Wingless pathway; Wnt-MB, Wnt-activated medulloblastoma; HDCx, Marrow-ablative chemotherapy; AuHPCR, Autologous hematopoietic progenitor cell rescue; CSI, Craniospinal irradiation; MRI, Magnetic resonance imaging; DWI, Diffusion-weighted imaging; CSF, Cerebrospinal fluid; GTR, Gross total resection; FISH, Fluorescence in situ hybridization; IHC, Immunohistochemistry; R1, First relapse; R2, Second relapse; R3, Third relapse; RT, Radiotherapy; OS, Overall survival

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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