



Multifocal medulloblastoma in an adult: a case report and review of the literature

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Abstract

Background Medulloblastoma (MB) is a highly aggressive tumor originating in the cerebellum, predominantly affecting children. Adult medulloblastoma is rare, leading to a lack of a standardized treatment protocol. Although multimodal strategies from pediatric MB have improved outcomes in adult patients, challenges persist, including early diagnosis difficulties, treatment toxicity, recurrence risks, targeted therapies, and controversies over chemotherapy timing and regimen.

Case description We present a clinical case involving a 53-year-old male patient diagnosed with multifocal medulloblastoma, who presented with symptoms of dizziness. Cranial magnetic resonance imaging (MRI) revealed space-occupying lesions in the right cerebellar infratentorial region and the right temporal pole, which were initially suspected to be meningiomas. The patient subsequently underwent surgical resection of the subtentorial lesion, which was pathologically confirmed to be a medulloblastoma. Molecular classification through genetic testing classified it as the SHH subtype. Postoperatively, the patient received sequential radiotherapy and chemotherapy. After radiotherapy, the lesion in the temporal pole disappeared, and the patient recovered well. Disease-free survival of this patient was more than 2 years, during which the patient returned to the hospital for follow-up every three months. Currently, the patient is in good condition with no significant treatment sequelae or signs of recurrence.

Conclusion Adult medulloblastoma is rare, and adult multifocal medulloblastoma is even rarer. The adult patient with multifocal medulloblastoma we report underwent surgery followed by sequential radiotherapy and chemotherapy, resulting in a favorable prognosis. This may suggest that postoperative radiotherapy combined with chemotherapy could be effective in controlling adult medulloblastoma.

Keywords Medulloblastoma · Adult Medulloblastoma · Multifocal Medulloblastoma · Sequential radiotherapy and chemotherapy

Introduction

Medulloblastoma (MB) is an aggressive tumor that occurs in the cerebellum and belongs to the family of primitive neuroectodermal tumors (PNETs) (Williams et al. 2019; Laneve

and Caffarelli 2020). As early as 1910, James Homer Wright first described MB as a unique central nervous system tumor and proposed that it might originate from restricted neuronal precursor cells, termed “neuroblasts” (Wright 1910). With the advent of the molecular era, many hypotheses regarding the cellular origin of MB have been challenged and refuted, including the assumption of originating from undifferentiated cells in the subventricular zone (Laneve and Caffarelli 2020). Despite extensive research over many years, the exact cellular origin of MB remains unclear, however, it is established that each subgroup of MB has different cellular origins (Sheng et al. 2024).

MB is one of the most common central nervous system malignancies in children but can also occur in adults (Yuile et al. 2022). In comparison, adult MB is very rare, with an

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annual incidence rate of approximately 0.6 cases per million people (Beier et al. 2018; Dirven et al. 2020; Spyridonidis et al. 2020), accounting for only 0.4–1% of adult central nervous system tumors (Kool et al. 2014; Dirven et al. 2020). The median age of MB in adults is between 20 and 40 years, mainly affecting young individuals under the age of 40 (Majd and Penas-Prado 2019), with case reports in patients over the age of 60 being particularly rare (Murase et al. 2018).

Moreover, MB usually occurs in the posterior fossa, a relatively hidden location, making its diagnosis and treatment more challenging (Liu et al. 2020). The clinical manifestations of patients are also not specific and are related to the location and size of the tumor. Common clinical manifestations include hydrocephalus, headache, dizziness, nausea, vomiting, unsteady gait, and truncal ataxia (Zaresharifi et al. 2024). Furthermore, since the radiological presentation of medulloblastoma is not consistent and an accurate conclusion cannot be drawn from imaging data alone, the gold standard for diagnosing medulloblastoma remains histopathological examination (Al-Halabi et al. 2011).

To date, MB is classified into four distinct histological subtypes: classic medulloblastoma, desmoplastic/nodular, extensive nodularity, and large cell/anaplastic (LC/A) (Eibl et al. 2021; Siegfried and Delisle 2021). At the molecular level, MB is also categorized into four molecular subtypes: WNT, SHH, Group 3, and Group 4 (Louis et al. 2021). CTNNB1 mutations are associated with the WNT subtype, PTCH/SMO/SUFU alterations correspond to the SHH subtype, MYC amplification or overexpression is linked to Group 3, and CDK6 as well as MYCN amplification is characteristic of Group 4. Further studies also found significant differences in treatment response and survival among MB patients with different molecular subtypes (Archer et al. 2017). For instance, the WNT subtype generally has a good prognosis (Brandes and Franceschi 2014), while the SHH subtype may benefit from molecular targeted therapy (Kool et al. 2014). However, for patients with mutations in the SMO downstream pathway, SMO inhibitors may be ineffective or develop resistance, necessitating the development of new strategies (Ramaswamy and Taylor 2017).

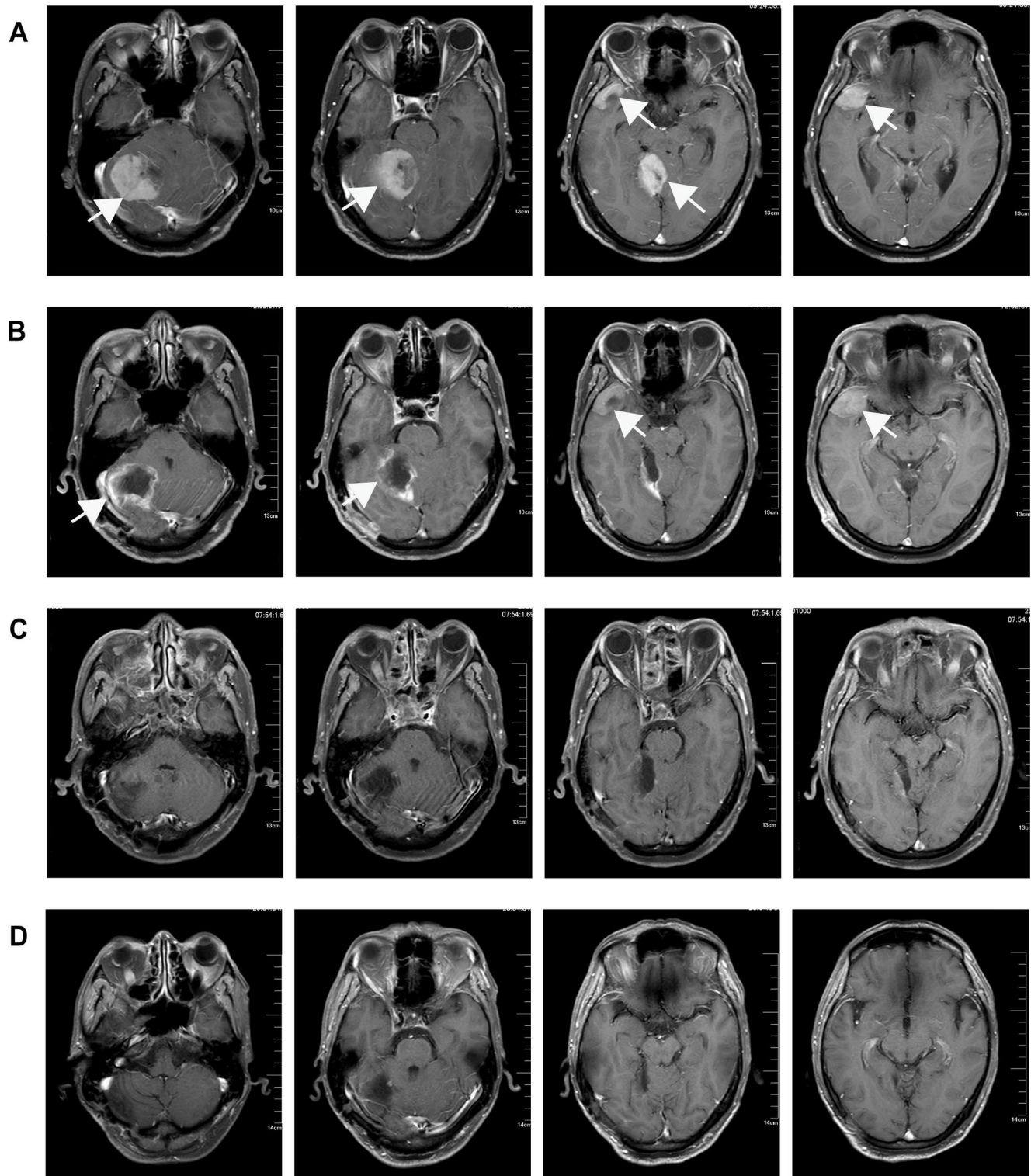
Given the exceedingly low incidence of adult MB, conducting prospective studies poses significant challenges and such studies are therefore scarce (Majd and Penas-Prado 2019). There are currently no established official treatment guidelines for medulloblastoma in adult patients. The treatment for adult MB are primarily extrapolated from data obtained from pediatric MB patient cohorts and retrospective analyses (Penas-Prado et al. 2020).

Fig. 1 MRI examination at different stages of treatment. (A) Preoperative MRI examination showed the lesions were located in the right infratentorial cerebellum and the right temporal skull (white arrows). The enhanced scan was not uniformly enhanced, and the lamellar low signal without intensification could be seen. (B) Postoperative MRI examination showed most of the right cerebellar lesions were removed. The lesion margin and adjacent dura were significantly enhanced (white arrows). In the right temporal skull, the sublamellar lesions were slightly larger than that before operation, with uneven enhancement (white arrows). The cerebellum and the fourth ventricle were slightly compressed, the supratentorial ventricle was slightly enlarged, and the midline structure was centered. (C) Postradiotherapy MRI examination showed the dural enhancement at the edge and adjacent to the right cerebellar operative area was less than before. There was no definite indication of the lesions in the right temporal skull. (D) After all treatments, MRI examination showed the right posterior cranial fossa changed after the operation, the right cerebellar hemispherical lamellar softening lesion formed and the surrounding gliosis. No significant enhancement was observed.

Case report

The patient, a 53-year-old male, presented to the hospital with dizziness accompanied by fatigue and poor appetite for over ten days. He first went to a local hospital and Computed Tomography (CT) examination of the head revealed intracranial space occupying lesions. Then he came to our hospital for further diagnosis and treatment. Upon admission, we conducted a detailed physical examination and did not find any obvious positive signs. There were no significant findings in his past medical history, personal history, or family history. Cranial magnetic resonance imaging (MRI) revealed two mass lesions: one located under the right cerebellar tentorium and the other beneath the inner table of the right temporal skull (Figure 1A). The lesions exhibited slightly elongated T2 and T1 signals, with isointense signals on DWI. The dimensions were approximately 44 mm × 45 mm × 43 mm and 27 mm × 20 mm × 26 mm (anteroposterior diameter × transverse diameter × craniocaudal diameter), respectively. The enhanced scan showed heterogeneous enhancement with band-like hypointense areas within the lesions that did not enhance, surrounded by slight elongation of T2 and T1 edema. The lesion had a broad base connected to the adjacent meninges, causing compression of the cerebellum and fourth ventricle, leading to tonsillar herniation, slight expansion of the supratentorial ventricles, and the midline structures were centered. Comprehensive examinations including chest CT, abdominal ultrasound, thyroid, and cervical lymph nodes did not reveal any other issues, ruling out distant metastasis.

After the imaging and hematology tests, he underwent a focal lesion excisional biopsy under general anesthesia. After removing a portion of the cerebellar tissue, revealing the lesion located at the posterior inferior aspect of the right cerebrum, with sizes approximately 44 mm × 45 mm × 43 mm. And more importantly, the tumor showed an



aggressive and invasive growth, indistinct borders from surrounding tissues. Intraoperatively, the cerebellar lesion was fully excised, and biopsies were obtained from the cerebellar tentorium for both frozen and permanent pathological analysis. In contrast, the lesion in the right temporal region was not resected. Immunohistochemistry staining according

to standard procedures demonstrated that the positive rate of the Ki-67 (marker of proliferation) index was about 40%, and positivity for CD6, Syn, Vimentin, CD99 and SOX-10 were observed. However, staining for CD34, S-100, SSTR-2, CgA, EMA, PR, CK, STAT-6, INI-1 and GFAP-1 were negative. Based on morphological and immunohistochemical

results, the diagnosis was consistent with MB. Tumor tissue was analyzed using a comprehensive approach that included Next-Generation Sequencing (NGS), Fluorescence In Situ Hybridization (FISH), and methylation-specific PCR. This analysis revealed an activating mutation in the SMO gene (p.L412F) and a deletion of chromosome 17. Notably, no mutations were detected in the TP53 or CTNNB1 genes, nor was there any amplification of the MYCN or MYC genes. Additionally, promoter region methylation of the MGMT gene was not observed, and co-deletion of 1p36 and 19q13 was absent. Based on the comprehensive pathological morphology and molecular testing results, the molecular subtype of this patient's MB was classified as SHH-4 group with a TP53 wild-type status.

One month after surgery, the patient underwent a cranial MRI examination (Figure 1B). Postoperative changes were observed in the right occipital skull and adjacent soft tissue, with the enhanced scan showing significant reinforcement at the lesion edges and adjacent dura mater. Slightly elongated T2 and T1 mass shadows were visible beneath the inner table of the right temporal skull, with a few long T1 and T2 signal shadows inside. The lesion measured approximately 32 mm × 20 mm × 26 mm (anteroposterior diameter × transverse diameter × craniocaudal diameter), representing an increase in size compared to preoperative measurements. The enhanced scan showed heterogeneous reinforcement, with band-like hypointense areas within the lesions that did not enhance. Small blood vessel shadows were observed in the perilesional area, accompanied by mild T2 and T1 signal prolongation indicative of surrounding edema. The lesion had a broad base connected to the adjacent meninges, causing slight compression of the cerebellum and fourth ventricle, slight expansion of the supratentorial ventricles, and the midline structures remained centered.

Subsequently, the patient began to receive craniospinal irradiation, with a dose of 36 Gy delivered in 18 fractions, once daily, five days per week. An additional 14 Gy was administered to the subtentorial tumor bed, increasing the total dose to 50 Gy; an additional 24 Gy was delivered to the right temporal pole lesion, resulting in a cumulative dose of 60 Gy. During radiotherapy, the patient experienced mild bone marrow suppression along with symptoms including headache, dizziness, and nausea. We administered symptomatic supportive treatments, which included managing myelosuppression, alleviating cerebral edema, controlling nausea and vomiting, and preventing seizures. These interventions significantly alleviated the patient's symptoms and gradually improved his overall condition. One month following the completion of radiotherapy, the patient returned for a follow-up visit. During this visit, the patient reported no significant symptoms, and the physical examination revealed no specific positive signs. A repeat cranial

MRI demonstrated that the enhanced scan showed reduced enhancement at the lesion edges and adjacent dura mater compared to the baseline images. The previously observed abnormal signals beneath the inner table of the right temporal skull were no longer observed (Figure 1C). Additionally, the compression of the cerebellum and fourth ventricle, as well as the expansion of the supratentorial ventricles, were notably alleviated compared to previous imaging.

After thorough evaluation, we have determined that the most appropriate course of action for the patient is to administer six cycles of chemotherapy using the Etoposide-Cisplatin regimen. Specifically, Etoposide was administered at a dose of 100 mg/m² intravenously on days one, two, and three, while Cisplatin was given at a dose of 80 mg/m² intravenously on day one. This treatment cycle was repeated every 3–4 weeks. Following chemotherapy, the patient experienced mild to moderate bone marrow suppression accompanied by symptoms such as nausea, vomiting, and reduced appetite. We provided targeted supportive care, which effectively alleviated the patient's symptoms and enabled him to complete six cycles of chemotherapy. After the end of all treatment (May 22, 2023), the patient returned for regular follow-up visits every three months. In the most recent follow-up on March 25, 2025, the patient's condition was good with no signs of recurrence or metastasis observed (Figure 1D).

Discussion

Adult multifocal medulloblastoma (MMB) is extremely rare, with the first documented case reported in 1988 (Shen and Yang 1988). To date, only seven cases have been reported (Shen and Yang 1988; Spagnoli et al. 1990; Gliemroth et al. 1998; Ciccarino et al. 2012; Balik et al. 2015; Saad et al. 2017; Troncon et al. 2020) (Table 1). After reviewing these literatures, we found that among the seven patients, there were four males and three females, with an average age of 39.9 years (range 31–54 years). All patients presented with 2 to 5 lesions. The common symptom reported by all patients was headache. Additional symptoms included dizziness, vomiting, gait disorder, intention tremor, dysmetria, ataxia and diplopia. The most common site of occurrence was the cerebellar hemisphere (7/7), consistent with the most common site for adult MB, followed by the cerebellar vermis (3/7), with other sites including the left occipital lobe, pontocerebellar angle, bilateral caudate nucleus, and left temporal lobe (Troncon et al. 2020). Unfortunately, only three patients (Balik et al. 2015; Saad et al. 2017; Troncon et al. 2020) underwent genetic testing, and all of them were confirmed to be SHH subgroup, the most common type of adult MB. One patient developed a rare

Table 1 Reported cases of multifocal Medulloblastomas in adults

Case, Gen- Year Age	Gen- der,	Num- ber of lesions	Clinical manifestation	Tumor location	Spinal metastasis	Molecular classification	TP-53 mutation	Prolifera- tive index (Ki-67)	Therapeutic regimen	Num- ber of surgical excisions	Chemotherapy regimen	Survival
1 1988 31	Male	3	Headache, vomiting	Cerebellar hemispheres	Unspecified	Unspecified	Unspecified	Unspecified	Surgery + Craniospi- nal radiation	3	-	Recurred 1 year later, recurred again after a second operation and died
2 1990 36	Female	3	Headache, gait disturbance, intention tremor, and nystagmus	Cerebellar hemispheres	No	Unspecified	Unspecified	Unspecified	Surgery + radiation	Unknown	-	Unspecified
3 1998 54	Male	2	Headache, nausea, vomit- ing, nystagmus, gait disorders, and bilateral dysmetria	Cerebellar hemi- spheres, left occipital lobe	No	Unspecified	Unspecified	Unspecified	Biopsy + Craniospinal radiation	0	-	Unspecified
4 2012 31	Male	2	Headache, ataxia	Cerebellar hemi- spheres, left occipital lobe	No	Unspecified	Unspecified	Unspecified	Surgery + 2 cycles of chemother- apy + craniospinal radiotherapy	2	Cisplatin + etopo- side + cyclofosfamide	No recur- rence after 6 months of follow-up
5 2015 39	Female	3	Headache	Cerebellar vermis, left hemisphere	Unknown	SHH	Unspecified	Unspecified	Surgery	Gross total tumor resection	-	Died of acute diffuse cerebellar swelling 12 days after surgery
6 2017 41	Male	5	Headache, dizziness	Cerebellar vermis and hemi- spheres, bilateral caudate nuclei, and left tempo- rale lobe	No	SHH	Negative	Unspecified	Biopsy	0	-	Unspecified
7 2020 47	Female	3	Headache, vomiting	Cerebellar vermis, cerebellar hemispheres	No	SHH	Negative	30-40%	Surgery + craniospinal radiation + 6 cycles of chemotherapy	2	Cisplatin + lomus- tine + vincristine	No progres- sion for 30 months after diagnosis

Table 1 (continued)

Case, Year	Gender, Age	Num-ber of lesions	Clinical manifestation	Tumor location	Spinal metastasis	Molecular classification	TP-53 mutation	Prolifera-tive index (Ki-67)	Therapeutic regimen	Num-ber of surgical excisions	Chemotherapy regimen	Survival
8/Our case	Male 53	2	Headache	Cerebellar hemisphere, right tempo-ral lobe	No	SHH	Negative	30-40%	Surgery + craniospinal radiation + 6 cycles of chemotherapy	1	Etoposide + cisplatin	No recur-rence after 22 months of follow-up

postoperative acute diffuse cerebellar swelling (DCS) and died 12 days after surgery (Balik et al. 2015). Our report is the eighth case, involving a 53-year-old male who presented with two lesions simultaneously, one located in the right subtentorial region of the cerebellum and the other in the right temporal pole; genetic testing confirmed it as the SHH subtype. Although the chemotherapy regimens used by the three patients receiving chemotherapy were not the same, it appears that the patients receiving chemotherapy seemed to have a better prognosis than those who did not.

Contrary to expectations, MMB in children appears to be less common than in adults, with only two cases have been reported. Smucker (Smucker and Smith 2006) et al. reported in 2006 on a 2.5 year old boy who presented with sexual clumsiness and difficulty walking. Multifocal connective tissue hyperplasia MB and Gorlin syndrome [also known as nevoid basal cell carcinoma syndrome (NBCCS)], were confirmed by pathologic findings, DNA sequencing, clinical manifestations and family history. His father had NBCCS, and his mother also had a history of large tumors in her family. MB is one of the secondary diagnostic criteria for NBCCS (Fujii and Miyashita 2014), and about 3% of NBCCS patients will develop MB (Smucker and Smith 2006). Ionizing radiation that treats MB may also cause basal cell carcinoma (BCC) to develop in the irradiated area over a long period of time (Campbell et al. 2005). In 2022, a 10-year-old boy with synchronous multifocal classic MB was reported, presenting with bilateral vision loss (Borni et al. 2022). MRI Showed 4 lesions with Spinal metastasis. This was the only one of the 9 patients with MMB with spinal metastasis. In general, MB is more prone to leptomeningeal dissemination rather than spinal cord metastasis (Goyal et al. 2018).

Although cases of MMB are rare and the clinical presentation is complex, the treatment of these patients follows the core treatment principles of MB. Currently, MB treatment includes surgical resection, radiotherapy, and chemotherapy, but there are certain differences between countries, regions, centers, and even within centers. Surgery is the preferred treatment method because it is the most effective means of relieving symptoms, as well as providing a definitive diagnosis and laying the foundation for subsequent treatment (Franceschi et al. 2019). The standard for surgery is maximal safe resection; however, if the lesion involves the brainstem, aggressive resection is not recommended (Choi 2023). The efficacy of radiotherapy is affirmative, whether it is received before, during, or after surgery, and it benefits patient survival (Ma et al. 2020). The appropriate dose for the tumor bed or posterior fossa is currently under discussion and related studies have found that in adults, a local radiotherapy dose exceeding 54 Gy can achieve a 70–90% 5-year disease control rate, while the

percentage significantly decreases when the dose is below 50 Gy (Brandes and Franceschi 2014).

With the standard implementation of this comprehensive treatment model, the five-year event-free survival rate for children with MB exceeds 60% and overall survival rate exceeds 70% (von Bueren et al. 2016). According to different risk stratifications, combined treatments have also shown promising results in adult MB patients (Hadi et al. 2018; Manfreda et al. 2023), with 5-year survival rates exceeds 60% (Eibl et al. 2021). Although there is no unified consensus on whether adult MB patients should undergo adjuvant chemotherapy, the timing and regimen of chemotherapy, statistical analyses have found that adult patients receiving postoperative radiotherapy combined with chemotherapy had improved outcomes compared to radiotherapy alone (Kann et al. 2017; Majd et al. 2021). A single-institution retrospective study indicated that adding chemotherapy during radiotherapy improved patients' PFS and OS, but the study included only average-risk adult patients (no metastasis and no residual lesions after surgery) (Franceschi et al. 2020). Additionally, Banu Atalar et al. found that chemotherapy was beneficial to local control and reduced local recurrence rate (Atalar et al. 2018). The commonly used chemotherapy regimen for adult MB is the Packer regimen (eight doses of vincristine 1.5 mg/m² [maximum of 2 mg] during radiotherapy, followed by a maximum of eight cycles of lomustine 75 mg/m² on day 1, cisplatin 70 mg/m² on day 1 and vincristine 1.5 mg/m² [maximum of 2 mg] on days 1, 8, and 15 of 6 week cycles) was developed with and without radiotherapy dose reduction (Franceschi et al. 2019). Cisplatin - etoposide regimen can be used as an alternative or for recurrence (Sherwood et al. 2023). The patient we report underwent sequential chemoradiotherapy postoperatively, with the cisplatin-etoposide regimen, which has so far been beneficial to the patient's survival. Combining previous reports with the cases we reported, we can find that it appears that surgery combined with craniospinal radiotherapy and 6 cycles of adjuvant chemotherapy are more beneficial for tumor control and survival in patients.

Unfortunately, those who survive long after the end of comprehensive treatment often experience severe side effects. The most common \geq G3 toxicities were ototoxicity, motor dysfunction, and cognitive dysfunction. Others include anxiety-depressive states, hypothalamic-pituitary dysfunction, and cranial nerve dysfunction. All of these significantly impairs their quality of life (Saraf et al. 2022). What's more, even if initial treatment is successful, about 30% of MB patients still experience tumor recurrence (Sheng et al. 2024). Late-stage relapses are more common in adult patients, which usually occurs more than 4 years after treatment (Troncon et al. 2020). Because of the potential risk

of relapse, long-term monitoring becomes an important part of the management of adult patient.

With the deepening understanding of the cell source, pathogenesis and subtype of medulloblastoma, personalized targeted therapy may become a reality in the future. Vismodegib is one of the currently approved SMO inhibitors, but it has not been widely adopted due to rapid development of resistance (Shih 2021). Meanwhile, reduced dose conventional radiotherapy, conformal radiotherapy, and proton radiotherapy are potential alternative radiotherapy approaches currently under exploration in some clinical trials. Maura Massimino and colleagues found that reduced-dose craniospinal irradiation combined with chemotherapy is feasible for adult patients with standard-risk (no distant metastases, postoperative residual lesions < 1.5 cm² or no residual lesions, non-large cell/anaplastic histology) medulloblastoma (Massimino et al. 2020). A small retrospective study showed that compared with photon craniospinal radiotherapy, proton craniospinal radiotherapy can better protect the surrounding organs at risk without compromising the efficacy, and is well tolerated, reducing the incidence of acute radiation-related toxicities (such as hematologic and gastrointestinal toxicities) (Breen et al. 2024).

In conclusion, synchronous MMB is quite rare in both adult and pediatric patients, with only 7 adult cases and 2 pediatric cases reported so far. Due to the limited number of cases reported in the literature, the pathogenesis and prognosis of MMB remains unclear. This study reports a case of MMB in an adult patient who received sequential radiotherapy and chemotherapy postoperatively and had a good prognosis. Moreover, this patient belongs to the most common SHH subtype of adult MB, providing a reference direction for a deeper understanding of the characteristics of adult multifocal MB and exploring more effective treatment options. Future research and clinical trials are needed to further explore personalized treatment plans to improve treatment outcomes, reduce the risk of recurrence, and enhance the quality of life for patients.

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Author contributions Cha Luo prepared the manuscript and figures. Fei Zhang, Hongting Jiang, Ying Zeng and Zhonglian Wang performed data analysis and interpretation. Qing Ye, Wei Jian and Jing Zhang contributed to discussion and interpretation. Cha Luo, Qiaofen Fu and Xiaofeng Zhu edited and approved the final manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval The studies involving humans were approved by the Ethics Committee of the First Affiliated Hospital of Kunming Medical University, under approval number (2024) Ethical L No. 119.

Patient consent for publication The patient provided written informed consent for publication of patient data and associated images.

Competing interests The authors declare no competing interests.

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