



Case Report



# Adult Medulloblastoma in Japan: Single Institutional Case Series with Literature Review

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## Abstract

Medulloblastoma in adults older than 20 years of age is extremely rare disease in Japan. We here report the clinical characteristics, tumor pathology including molecular classification, treatment and prognosis of 3 cases of patients with adult medulloblastoma and discuss the clinical issues.

Three female patients, aged 28, 35 and 48 years, presented with intracranial hypertension, vertigo and cerebellar ataxia. The tumors, which were relatively well-demarcated and irregularly contrasted were located in the cerebellar vermis in one patient and in the cerebellar hemisphere in the two patients. All patients underwent subtotal or greater resection. The pathological diagnosis was classic type medulloblastoma and the molecular classification was Group 4, SHH-TP53 wildtype and Wnt/ $\beta$ -catenin (WNT). Whole-brain and whole-spinal irradiation was performed, followed by ICE (Ifosfamide, Cisplatin and Etoposide) chemotherapy. Two patients with a hemispheric tumor showed no recurrence and had a favorable clinical course, whereas the patient with a vermis tumor with a small residual tumor in the brainstem developed multiple spinal metastases and cerebrospinal fluid dissemination within 2 years after the surgery.

In the EU and the United States, guidelines for the treatment of adult medulloblastoma have been established, which recommend the addition of craniospinal irradiation protocols and multi-agent chemotherapy according to the clinical risk of each patient, determined by the pathological diagnosis and molecular classification. In Japan, there have been only a few case reports of adult medulloblastoma and both basic and clinical research has not substantially progressed. Therefore, the establishment of medical practice guidelines for adult medulloblastoma urgently needed in Japan.

**Keywords:** Adult Medulloblastoma; ICE Chemotherapy; Clinical Guidelines; Molecular Classification; Pathological Diagnosis

## Introduction

Medulloblastoma is the most common type of embryonal tumor, with 80% of cases occurring in individuals of infancy to school age and it is 1.85 times more likely to occur in boy than in girls. The cerebellar vermis and fourth ventricle account for 90% of the tumor sites and the disease is characterized by symptoms of intracranial hypertension and truncal ataxia [1].

The Brain Tumor Registry Japan (2005-2008), which registered 16,722 cases of primary brain tumors, contained only 139 cases (0.8%) medulloblastoma, of which only 22 cases (15.3%) were patients of adult onset (older than 20 years) [1]. As this registry contains cases newly diagnosed during a 4-year period, this indicates that only an average 5.5 cases of medulloblastoma are diagnosed in adults per year in Japan [1]. On the other hand, 965 cases of medulloblastoma were registered in SEER (Surveillance,

Epidemiology and End Results Program) (1992-2013) and although the median age of onset was 9 years, which is similar to that in Japan, 349 patients (36.2%) were older than 20 years, showing a 2.4-times higher adult incidence rate than in Japan [2]. In CBTRUS (The Central Brain Tumor Registry of the United States) (2011-2015), 65 cases of medulloblastoma patients aged 20 years or older were registered annually, which corresponds to an adult incidence rate that is 4 times higher than that in Japan, considering the population ratio [3]. We believe that this difference in epidemiological data may be a reason for the lack of progress basic and clinical research on adult medulloblastoma in Japan compared with in Europe and the United States. The authors recently encountered three cases of adult patients with medulloblastoma. In this paper, we would like to review the clinical reports of adult medulloblastoma in Japan and raise some issues, particularly regarding treatment.

## Case Presentation

### *Case 1*

A 28-year-old woman presented with sudden onset of headache and nausea and was referred to our hospital. A CT scan displayed a well-demarcated, slight high-density tumor with a necrosis-like low density area in the cerebellar vermis, together with obstructive hydrocephalus. MRI displayed a relatively homogeneously enhanced tumor with restricted diffusion. Gadolinium-enhanced MRI of the entire spinal cord displayed no obvious disseminated lesions. The preoperative diagnosis was ependymoma or pilocytic astrocytoma in the cerebellar vermis. A craniotomy was performed immediately and a subtotal resection was performed except for a small portion that infiltrated the floor of the fourth ventricle. The patient's hydrocephalus improved in the early postoperative period and her neurological symptoms have also shown a gradually improvement. However, postoperative imaging displayed a small residual tumor, less than 1 cm<sup>3</sup> in volume, at the floor of the fourth ventricle. The morphological diagnosis of the excised tissue was classic type medulloblastoma with dense proliferation of carrot-shaped tumor cells and distinct Homer-Wright rosettes, synaptophysin positive and GFAP negative. The molecular classification was Group 4. Postoperatively, the patient underwent radiation of 23.4 gray (Gy)/13 fraction (Fr) on the whole brain and spine with 28 Gy/14 Fr boost on the posterior fossa and a total of 15 cycles of the Ifosfamide, Cisplatin and Etoposide (ICE) regimen (ifosfamide: 900 mg/m<sup>2</sup>, days 1-5; cisplatin: 20 mg/m<sup>2</sup>, days 1-5; and etoposide: 60 mg/m<sup>2</sup>, days 1-5) as chemotherapy. Although CTCAE (Common Terminology Criteria for Adverse Events) grade 4 myelosuppression occurred from the fourth cycle, it was treated by G-CSF administration and her Karnofsky Performance Status (KPS) was maintained at above 70. However, 2 years after the initial surgery, the patient complained of back and hip pain and contrast-enhanced whole spinal MRI displayed extensive Cerebrospinal Fluid (CSF) dissemination and vertebral metastasis. Thereafter, best supportive care was selected and the patient died 3 years after the initial surgery.

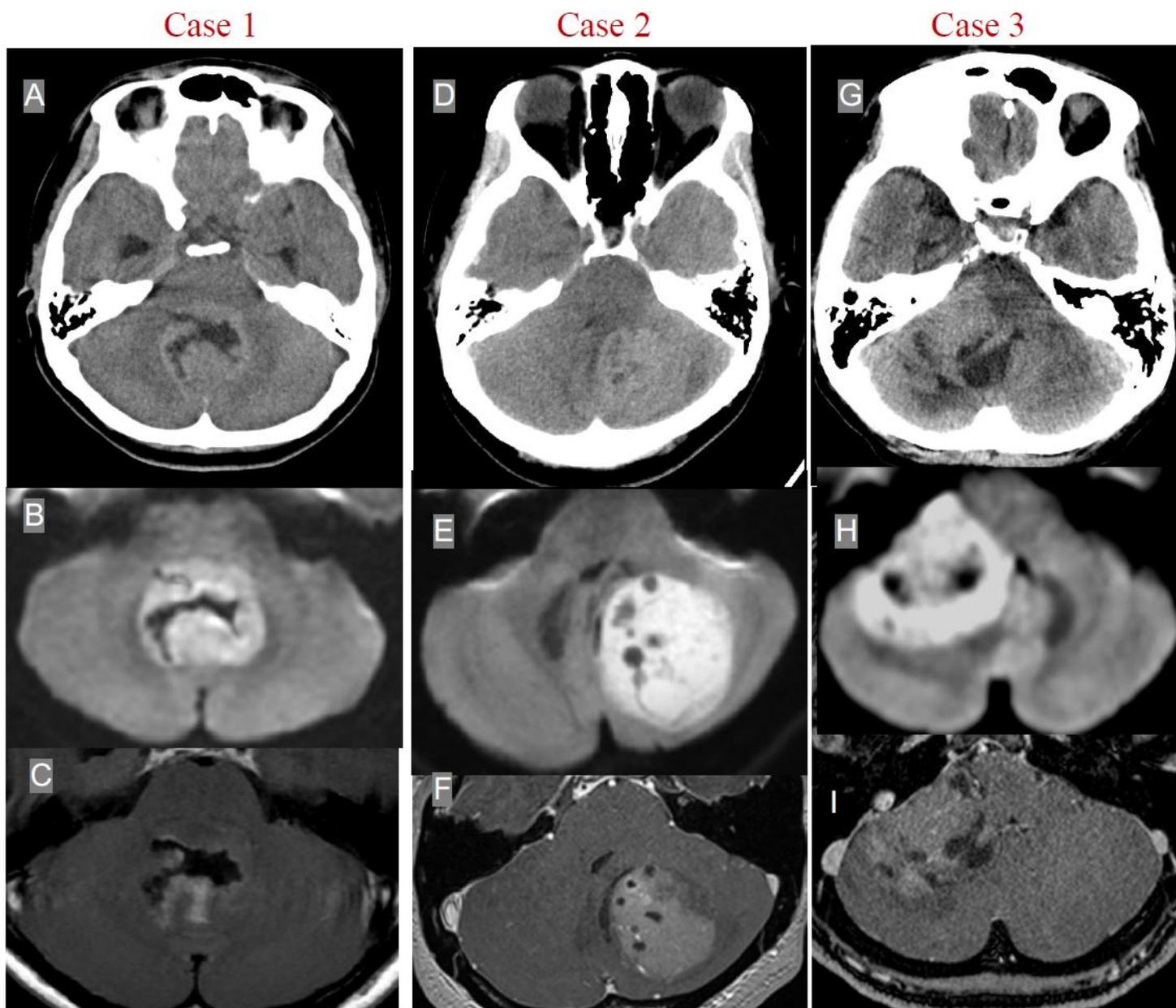
### *Case 2*

A 35-year-old woman was referred to the emergency department of our hospital with sudden onset of headache and nausea while at work. A CT scan displayed a well-demarcated, slight high-density tumor containing cyst-like low-density areas in the left cerebellar hemisphere and MRI displayed a tumor with relatively clear boundaries, including some cysts, diffusion restriction and strong enhancement with gadolinium. Gadolinium-enhanced MRI of the entire spinal cord displayed no obvious tumor dissemination. The preoperative diagnosis was possible pilocytic astrocytoma or solitary fibrous tumor. A craniotomy was performed and relatively well-defined tumor was removed completely. The excised tissue was a mixture of dark areas with dense proliferation of carrot-shaped tumor cells and Homer-Wright rosettes and pale nodules composed of synaptophysin-positive tumor cells. The latter tumor cells showed no nuclear migration of  $\beta$ -catenin and no proliferation of reticular fibers. Dark areas of tumor were GFAP positive, with a high Ki-67 positivity rate and the morphological diagnosis was classic medulloblastoma. The molecular classification of the tumor was the Sonic Hedgehog (SHH) type, TP53 wildtype, CTNNB1 (exon 3) wildtype and TERT promoter (exons 2 - 11) wildtype. Postoperative imaging displayed no residual tumor and the patient underwent irradiation of 23.4 Gy/13 Fr on the whole brain and spine with 30.6 Gy/17 Fr boost on the posterior fossa and 6 cycles of chemotherapy with the ICE regimen. Five years after surgery, her KPS was 100, no apparent local recurrence or CSF dissemination.

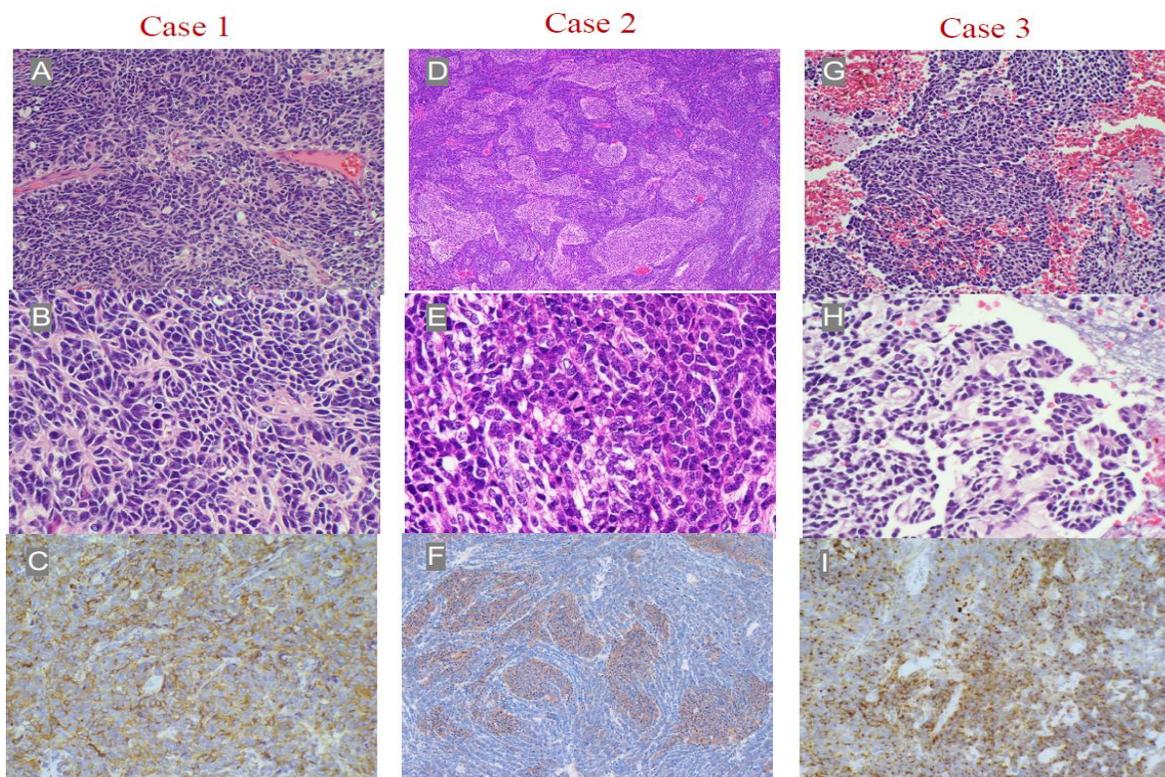
### *Case 3*

A 48-year-old woman presented to the otorhinolaryngology clinic of our hospital complaining of slowly progressive hearing loss and underwent a head MRI, which displayed a tumor in the right cerebellopontine angle. The patient was referred to our department and scheduled for surgery. However, she rapidly developed gait disturbance, dysarthria and headache and a CT scan displayed a rapid growth of the tumor, so she underwent emergency surgery. Preoperative MRI displayed a well-

demarcated, diffusion-restricted, irregularly weakly enhanced tumor within the right middle cerebellar peduncle to the cerebellar hemisphere and the preoperative diagnosis was high-grade glioma. The reddish-gray colored tumor had a relatively clear boundary and was easily removed totally. Pathological analysis demonstrated dense proliferation of carrot-shaped tumor cells, with scattered Homer-Wright rosettes, synaptophysin positive and GFAP positive. The final pathological diagnosis was classical medulloblastoma. The molecular analysis indicated that the tumor was the WNT type. Postoperative imaging displayed no obvious residual tumor in the cerebellar peduncle to the hemisphere and a search of the entire spinal cord showed no obvious CSF dissemination. The patient underwent irradiation of 36 Gy/18 Fr on the whole brain with 30.6 Gy/17 Fr on the whole spine and 10 cycles of chemotherapy with the ICE regimen. Eleven years after the surgery, her KPS was 70, with no apparent local recurrence or CSF dissemination (Fig. 1-3).



**Figure 1:** Preoperative neuroimages of the three cases. A, D, G: plain CT scan images: B, E, H: diffusion-weighted MRI images: C, F, I: gadolinium contrast T1-weighted MRI images. In all three patients, plain CT scans displayed a faint high-density lesion (A, D, G), diffusion-weighted MRI images displayed severe diffusion restriction (B, E, H) and gadolinium contrast T1-weighted MRI images displayed faint irregular enhancement effects (C, F, I).



**Figure 2:** Histopathological findings of the tumors from the three cases. A, D, G: hematoxylin and eosin staining (X 100); B, E, H: hematoxylin and eosin staining (X200). C, F, I: immunostaining using an anti-synaptophysin antibody (X 100). In all three cases, there was dense proliferation of immature cells with carrot-shaped nuclei and scanty cytoplasm. In cases 1 and 3, typical Homer-Wright rosettes were observed. Case 2 had some nodular regions, but the main pattern was diffuse, so it could not be classified as extensive nodularity. Synaptophysin staining was positive in all three patients, although the degree of staining varied.



**Figure 3:** Postoperative neuroimages of the three cases. A, E, H: gadolinium contrast T1-weighted MRI images of the brain: B, F, I; gadolinium contrast T1-weighted MRI images of the spine: C: whole-body gallium scintigraphy: D, G: diffusion weighted MRI images. Case 1 displayed local recurrence and CSF dissemination at two years postoperatively, as well as multiple metastases to lymph nodes and spinal vertebrae. Cases 2 and 3 have shown favorable long-term follow-up results with no recurrence.

## Results: Case Summary

One issue common to all three cases was that medulloblastoma was not included as a preoperative differential diagnosis. Case 1 was a 28-year-old patient with a tumor arising in the cerebellar vermis, but the tumor was well demarcated, so we thought it was a pilocytic astrocytoma or an ependymoma. Cases 2 and 3 were patients in their thirties and forties with intra-cerebellar hemispheric tumors and the preoperative diagnosis was pilocytic astrocytoma or high-grade glioma. However, all three patients had tumors with slightly high density without calcification on CT and marked diffusion restriction and an irregular, weak contrast enhancement, which are characteristics of medulloblastoma. The morphological diagnosis of the tumors of all three patients was classic medulloblastoma, with dense proliferation of carrot-shaped tumor cells and a typical Homer-Wright rosettes. The tumor of case 2 contained nodules with strong neuronal differentiation, but the findings were not considered prominent enough to be diagnosed as medulloblastoma with extensive nodularity. Molecular classification varied between Group 4, SHH-TP 53 wildtype and WNT. Regarding treatment, all patients underwent radiation therapy of whole brain and whole spinal cord, followed by the ICE regimen for as long as possible, which was terminated in two patients owing to adverse events. Eventually, case 1, in whom a small piece less than 1 cm<sup>3</sup> in volume of the infiltrating tumor remained in the floor of the fourth ventricle, developed early recurrence, resulting in death. On the other hand, cases 2 and 3 had tumors of hemispheric origin that were surgically removed completely, resulting in favorable control (Table 1,2).

	Case 1	Case 2	Case 3
Age (years) / sex	28 / female	35 / female	48 / female
Symptoms	Headache, nausea	Headache, nausea	Hearing disturbance, headache
Location	Cerebellar vermis	Cerebellar hemisphere	Cerebellar hemisphere
CT scan	Heterogeneous slight high density without calcification	Heterogeneous slight high density without calcification	Heterogeneous slight high density without calcification
MRI	Restricted diffusion and heterogeneous enhancement	Restricted diffusion and heterogeneous enhancement	Restricted diffusion and heterogeneous enhancement
Extent of resection	Subtotal resection	Total resection	Total resection
Pathological/ molecular diagnosis	Classic medulloblastoma, Group 4	Classic medulloblastoma, SHH-TP53 wildtype	Classic medulloblastoma, WNT
Residual tumor	1 cm <sup>3</sup> in the floor of the fourth ventricle	None	None
Radiotherapy	Whole brain and spine (23.4Gy/13Fr) and posterior fossa boost (28Gy/14Fr)	Whole brain and spine (23.4Gy/13Fr) and posterior fossa boost (30.6Gy/17Fr)	Whole brain (36Gy/18Fr) and whole spine (30.6Gy/17Fr)
Chemotherapy	ICE, 15 cycles	ICE, 6 cycles	ICE, 10 cycles
Recurrence	Focal recurrence	None	None
CSF dissemination/ metastasis	CSF dissemination and multiple vertebral metastasis	None	None
Prognosis	Dead, 3 years after initial surgery	Alive, 5 years after initial surgery	Alive, 11 years after initial surgery

**Table 1:** Summary of the clinical characteristics, pathological findings, treatment details and clinical course of the three cases

Author (year)	Age (years)/sex	Tumor location	CT	MRI	Preoperative diagnosis	Extent of resection	Histopathological diagnosis	Molecular classification	Radiotherapy	Chemotherapy	Prognosis
Miyata H, et al. (1998)	43/ female	Hemisphere	Low density lesion	T2 high intensity lesion, poor enhancement	NA	NA	Medulloblastoma with neuronal differentiation	NA	NA	NA	NA
Ueba T, et al. (2006)	19/ female	Hemisphere	NA	T2 isointensity lesion, DWI high intensity lesion, nodular enhancement	NA	Total resection	Desmoplastic medulloblastoma	NA	NA	NA	NA
Yoshimura J, et al. (2009)	25/ female	Hemisphere	NA	T2 high intensity lesion, DWI high intensity lesion, no enhancement	Focal brainstem glioma	Partial resection	Classic medulloblastoma	NA	Craniospinal irradiation	Systemic chemotherapy	Complete remission for more than 2 years
Murase M, et al. (2018)	63/ female	Vermis	NA	T2 high intensity lesion, DWI high intensity lesion, no enhancement	Ependymoma, low-grade glioma, choroid plexus papilloma	Subtotal resection	Classic medulloblastoma	Group 4	Craniospinal irradiation	ICE, 3 cycles	Alive, 15 months after initial surgery
Akimoto J, et al. (2024)	28/ female	Vermis	High density lesion	T2 high intensity lesion, DWI high intensity lesion, weak enhancement	Pilocytic astrocytoma, ependymoma	Subtotal resection	Classic medulloblastoma	Group 4	Craniospinal irradiation	ICE, 15 cycles	Dead, 3 years after initial surgery
Akimoto J, et al. (2024)	35/ female	Hemisphere	High density lesion	T2 high intensity lesion, DWI high intensity lesion, weak enhancement	Pilocytic astrocytoma, solitary fibrous tumor	Total resection	Classic medulloblastoma	SHH-TP53 wildtype	Craniospinal irradiation	ICE, 6 cycles	Alive, 5 years after initial surgery
Akimoto J, et al. (2024)	48/ female	Hemisphere	High density lesion	T2 high intensity lesion, DWI high intensity lesion, weak enhancement	High-grade glioma	Total resection	Classic medulloblastoma	WNT	Craniospinal irradiation	ICE, 10 cycles	Alive, 11 years after initial surgery

NA: not assessed

**Table 2:** Summary of the reported cases of adult medulloblastoma from Japan.

## Discussion

In recent years, there has been a trend in Japan to concentrate patients with pediatric brain tumors in hospitals specializing in pediatric neurosurgery and hence general hospitals, including university hospitals, no longer encounter patients with medulloblastoma. Therefore, when we identify intramedullary cerebellar tumors in adults on neuroimaging, we rarely consider the possibility of medulloblastoma. If the vermis or the fourth ventricle is involved, we consider of the possibility of ependymoma, choroid plexus tumor or pilocytic astrocytoma and if the hemisphere is involved, we consider the possibility of hemangioblastoma, high-grade astrocytoma, primary central nervous system lymphoma or metastatic tumor as radiological differential diagnoses. Therefore, few doctors are able to consider medulloblastoma arising in the cerebellar hemispheres, which is more common in adults than in children, as a differential diagnosis for the posterior fossa tumors. The common imaging features observed in these three cases, including high tumor cell density, tissue heterogeneity and relatively well-defined borders, should be noted by neurosurgeons as they may aid in the differential diagnosis of medulloblastoma [4-7].

In cases of medulloblastoma in the cerebellar vermis of children, the classical Chang's clinical stage is still used today, with emphasis on the "M stage" that mainly evaluates CSF dissemination or metastasis [8]. However, in adult patients in whom the tumor is more likely to develop in the cerebellar hemispheres, it is unlikely that these tumors will spread to the fourth ventricle or invade the brain-stem, unless they become very large and in many cases there is a tendency for exophytic growth on the cerebellopontine angle side. There are also papers that refer to adult cases, such as "Cerebellopontine angle medulloblastoma" and "extra-axial medulloblastoma" [9-11]. When the tumor is removed surgically, it is often relatively well-defined and easy to remove, as shown in the present imaging findings and hence there is less risk of tumor cells being scattered into the CSF during surgery than in cases where the vermis is involved and there is also less risk of residual tumor cells. In fact, in case 1, the tumor originated in the cerebellar vermis, with a small amount of residual tumor in the brain-stem and early dissemination of the tumor into the CSF and hematogenous metastasis occurred. On the other hand, in cases 2 and 3, in whom the tumor originated in the cerebellar hemisphere, the tumor was completely removed and the patients showed a favorable treatment response. In other words, our present cases indicate that Chang's clinical stage may not be as clinically important as in pediatric cases, where vermis occurrence is more common for determining the prognosis of adult medulloblastoma and that the location of the tumor is an important prognostic factor [12,13].

The molecular five-classification system for pediatric medulloblastoma has been extensively studied, particularly regarding its association with clinical features and treatment prognosis. On the other hand, regarding the molecular classification of adult medulloblastoma, the number of cases is not as abundant as in pediatric cases. To the best of the authors' knowledge, no reports clearly demonstrated the association with clinical features or treatment prognosis as clearly as in pediatric cases. Wong, et al., performed molecular classification of 99 adult patients with medulloblastoma aged 18 years or older and noted that 49 (49.5%) were the SHH type, 19 were the WNT type and 31 were Groups 3 and 4 [14,15]. Of the 41 patients aged 30 years or older, 28 (68.3%) were the SHH type, 6 were the WNT type and 7 were Groups 3 and 4, demonstrating that the older the age of onset, the higher the proportion of the SHH type [15]. Regarding the mechanism of cerebellar development, the SHH signaling pathway gene cluster expressed in the upper rhombic lip during the embryonic period is thought to actively produce Granule Neural Precursors (GNP) from its geminal center, forming Purkinje cells and the external granular layer and further contributing to the formation of the internal granular layer [15,16]. In other words, the SHH type, which is found in approximately 70% of adult medulloblastomas, is thought to arise owing to cancer gene mutations, constitutive activation of the SMO gene or loss of PTCH1 in GNP, which should normally form the external granular layer, leading to increased cerebellar hemisphere development [15-19]. Therefore, the predominant type of adult medulloblastoma is the SHH type arising from the cerebellar hemispheres. Compared to cases arising from the vermis, these tumors are more readily resectable in their entirety. Furthermore, their lack of contact with the ventricular system results in fewer cases of cerebrospinal fluid dissemination, making them tumors with a favorable prognosis.

In Europe and the United States, clear treatment guidelines for adult medulloblastoma have been established. The NCCN (National Comprehensive Cancer Network in USA) clinical practice guidelines in oncology states that patients should be divided into groups of standard risk for recurrence and high risk for recurrence, according to the degree of surgical resection, presence of CSF dissemination or metastases and tumor histology and then the dose of craniospinal radiation or systemic chemotherapy should be determined [20,21]. The EANO-EURACAN clinical practice guidelines state that patients should be classified into two groups, intermediate risk and high risk, based on tumor histology and molecular classification, in addition to clinical factors such as residual tumor volume and presence of metastases, to determine the dose of craniospinal radiation and the need for concomitant or maintenance chemotherapy [22]. The intermediate risk group in this classification is defined as tumors with classic or desmoplastic histology with the molecular classification WNT or SHH p53-wild and the high risk group is defined as tumors with large cell or anaplastic histology with the molecular classification Group 4 or SHH p53-mutant [20-22]. The recommended systemic chemotherapy regimen in both guidelines is the A regimen (CCNU/CDDP/VCR) or the B regimen (CDDP/VCR/cyclophosphamide) is recommended for pediatric patients by Packer, et al., each of which is used for 8 cycles [23]. However, as adverse events associated with VCR are more likely to occur in adults than in children, it is acceptable to omit VCR from the both regimen when treating adults [21,22]. In Japan, there are no guidelines specifying such clear chemotherapy regimens or maintenance therapy durations. Consequently, the authors had no choice but to continue maintenance chemotherapy in a trial-and-error manner, after obtaining full informed consent from patients and their families. As a result, case 1 required maintenance chemotherapy for 15 cycles and case 3 required for 10 cycles. Fortunately, no adverse events such as nephrotoxicity occurred, however, it cannot be denied that the prolonged hospitalization period and the increased risk of adverse events stemmed from the authors' independent decision not to adhere to the guidelines [23.]

The authors were only able to find four reported cases of adult medulloblastoma in Japan (Table 2) [24-27]. All seven cases, including the three reported here, were female cases, ranging in age from 19 to 63 years (median 35), with no evidence of older age in the cases with hemispheric tumors. Five patients had tumors of cerebellar hemispheric origin and their imaging findings were consistent with those described above, with a sufficient degree of resection and a favorable clinical course. Molecular classification was only performed in four patients and was variable, with WNT and SHH-p53 wild in one patient each and Group 4 in two patients [27]. Postoperative adjuvant therapy included craniospinal irradiation in 5 patients, systemic chemotherapy in 5 patients together with the ICE regimen in 4 of the patients. In Japan, there are few options of anticancer agents that can be used for central nervous system embryonal tumors owing to medical insurance restrictions, in particular CCNU used in the Packer regimen is not covered by insurance and facilities treating adult brain tumors have limited experience using cyclophosphamide [23]. The use of the Packer regimen is considered to be difficult owing to these reasons. Therefore, for adult medulloblastoma patients in Japan, the ICE regimen that is used for germ-cell tumors in the intermediate to unfavorable prognosis group is often used. However, reports in Japan of the use of ICE regimens in addition to postoperative radiation for 6 to 8 cycles in children with medulloblastoma has not been possible to demonstrate the treatment outcomes comparable to Western reports [28-30]. In

the future, Japan should establish precise guidelines for the diagnosis and treatment of adult medulloblastoma, similar to those in Europe and the United States and guide primary physicians on radiation therapy and useful systemic chemotherapy regimens based on case risk classification.

### Conclusion

In the diagnosis and treatment of medulloblastoma occurring in adults aged 20 years or older, it is considered essential to recognize the imaging characteristics, perform a diagnosis that includes molecular classification based on histological type and administer postoperative adjuvant therapy appropriately. The first step is to collect more cases in Japan and conduct detailed analyses of the case's clinical conditions and treatment outcomes. Furthermore, it is considered urgent to establish clinical practice guidelines specifically in Japan, which comprehensively cover the clinical presentation, imaging findings and molecular pathological classification of adult medulloblastoma, to enable appropriate postoperative adjuvant therapy selection similarly to in Europe and in the US.

### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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### Data Availability Statement

Not applicable.

### Ethical Statement

The study was declared in CHU of Bordeaux ethic committee.

### Informed Consent Statement

All patient agreed to participate and signed an informed consent.

### Authors' Contributions

All authors contributed equally to this paper.

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