Original Article

Clinical outcome, radiological findings, and genetic features of IDH-mutant brainstem glioma in adults

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Summary

Background: With the recent advent of genetic testing, IDH-mutant glioma has been found among adult brainstem gliomas. However, the clinical outcome and prognosis of IDH-mutant brainstem gliomas in adults have not been elucidated. This study aimed to investigate the clinical outcome, radiological findings, and genetic features of adult patients with IDH-mutant diffuse brainstem gliomas.

Methods: Data from adult patients with brainstem glioma at Hokkaido University Hospital between 2006 and 2022 were retrospectively analyzed. Patient characteristics, treatment methods, genetic features, and prognosis were evaluated.

Results: Of 12 patients with brainstem glioma with proven histopathology, 4 were identified with IDH mutation. All patients underwent local radiotherapy with 54 Gray in 27 fractions combined with chemotherapy with temozolomide. Three patients had IDH1 R132H mutation and one had IDH2 R172G mutation. The median progression-free survival and overall survival were 68.4 months and 85.2 months, respectively, longer than that for IDH-wildtype gliomas (5.6 months and 12.0 months, respectively). At the time of initial onset, contrast-enhanced lesions were observed in two of the four cases in magnetic resonance imaging.

Conclusion: As some adult brainstem gliomas have IDH mutations, and a clearly

different prognosis from those with IDH-wildtype, biopsies are proactively considered to confirm the genotype.

Keywords: IDH-mutant, brainstem, glioma, astrocytoma, DIPG, MRI

Introduction

Brainstem gliomas are relatively rare tumors of the central nervous system and are more common in children [30]. They rarely occur in adults, with a frequency of less than 2% of all brain tumors [29]. Adult brainstem gliomas occur most commonly in the pons (60–63%), followed by the medulla oblongata (25%) and the midbrain (12–15%), with a combination of these brain structures being involved in most cases [10].

Recently, focus on specific genetic mutations in the pathological identification of primary brain tumors has amplified. According to the 2016 World Health Organization (WHO) classification system, the term "diffuse midline glioma (DMG), H3K27M-mutant" encompasses all diffuse gliomas situated in any midline structure of the brain and spinal cord exhibiting a lysine-to-methionine mutation at codon 27 within genes encoding histone 3 isoforms [24]. These mutations frequently manifest in gliomas, affecting the brainstem and cerebellum in pediatric patients, and entailing a notably unfavorable prognosis [1,7,13,19,22,26,37]. In the updated 2021 WHO classification system, it has evolved into "diffuse midline glioma, H3K27-altered" [25].

Further, mutation in isocitrate dehydrogenase 1 (IDH1) or isocitrate dehydrogenase 2 (IDH2) genes represent common genetic changes observed in diffusely infiltrating gliomas in adults [4,14,15,40,42]. The revised 4th edition of the 2016 WHO

classification of brain tumors established the presence of these mutations as a defining criterion for two distinct categories of diffuse gliomas with varying WHO grades, namely astrocytoma, IDH mutant, and oligodendroglioma, IDH mutant and 1p/19q co-deleted [24]. These mutations primarily manifest within the cerebral hemisphere, their occurrence in the infratentorial region, including the brainstem, being exceedingly rare [11,16,20].

Although initially believed to be nearly absent in diffuse brainstem gliomas, IDH mutations have indeed been reported, though at notably low frequencies, in diffuse brainstem gliomas [44]. However, relevant data are limited, particularly concerning the molecular characteristics, radiological findings, and clinical characteristics of these mutations in diffuse brainstem gliomas.

Herein, we aimed to present the clinical features of adult patients with IDH-mutant diffuse brainstem gliomas.

Methods and Materials

Study population

In this retrospective study, we included all adult patients (older than 18 years of age) diagnosed with brainstem glioma, based on pathological findings, and treated at Hokkaido University Hospital between 2006 and 2022. The patients who had not been evaluated for any histopathological assessment were excluded. Patient data, including clinical course, radiological imaging findings, treatment outcome, and pathological findings, were retrospectively analyzed by referring to their medical records. Using pathological findings and genetic information, an integrated diagnosis based on the revised 5th edition (in 2021) of the WHO classification of central nervous system (CNS) was made by a certificated neuropathologist. All manipulations were performed with approval from our institutional review board (018-0363). Since the study was retrospective, the requirement for informed consent was waived. Progression-free survival (PFS) was defined as the period between primary treatment and the first tumor recurrence on magnetic resonance imaging (MRI). Overall survival (OS) was calculated from the day of primary treatment to that of death.

Genetic analysis

DNA/RNA was extracted from frozen tumor tissues using AllPrep DNA/RNA Mini Kit (Qiagen, Tokyo, Japan) in accordance with the manufacturer's recommendations. Mutation hotspots at codons 27 and 34 of H3F3A, the TERT promotor (C228T and C250T), codon 132 of IDH1, and codon 172 of IDH2 were screened using Sanger sequencing, as described previously [17]. CDKN2A/B homozygous deletion and 1p19q co-deletion were analyzed by multiplex ligation-dependent probe amplification (MLPA) [2].

Statistical analysis

Data analysis was performed using GraphPad Prism (Version 10.1.0, GraphPad Software). The Kaplan–Meier method was used for survival analysis with 95% confidence intervals. To compare Kaplan–Meier curves, the log-rank was utilized.

Results

Patient demographics

Of the 12 patients histologically diagnosed with adult brainstem glioma between 2006 and 2022, 10 underwent histopathological investigation either prior to treatment, one at recurrence, or one at autopsy. We identified four patients diagnosed with IDH-mutant brainstem glioma, and four diagnosed with "diffuse midline glioma, H3K27M-mutant." Three patients had no hot spot mutations in IDH1/2 and H3F3A. One case was excluded as the specimen was in poor condition and could not be evaluated by DNA sequencing.

In this study, we classified the patients into two groups, according to the status of IDH1/2, namely IDH-mutant (IDH-mut group, four patients) and IDH-wildtype (IDH-WT group, seven patients). IDH-WT group included four patients with "diffuse midline glioma, H3K27M-mutant."

Clinical characteristics of brainstem glioma with IDH mutation

While Table 1 summarizes the clinical characteristics, Table 2 delineates the clinical outcomes and genetic features of IDH-mutant brainstem glioma. The average age at onset of the IDH-mut group was 31±6 years. All patients received chemoradiation therapy; two underwent pre-treatment biopsies for tissue diagnosis, one had a biopsy upon recurrence,

and one underwent autopsy following demise. Chemotherapy used temozolomide (TMZ) for all patients, and three patients were administered bevacizumab (Bev) at the time of recurrence. Radiotherapy comprised localized irradiation with 54 Gray in 27 fractions (Gy/27Fr) for all patients. The patients were re-diagnosed according to the latest 2021 WHO classification revision. In the two patients biopsied at the time of onset, one was categorized as "Astrocytoma, IDH-mutant, CNS WHO grade 2," and the other as "Astrocytoma, IDH-mutant, CNS WHO grade 3." The two patients biopsied at recurrence or autopsied were categorized as "Astrocytoma, IDH-mutant, CNS WHO grade 4." Three patients exhibited IDH1 R132H mutation while one presented IDH2 R172G mutation. None of the patients displayed co-mutations in H3F3A or HIST1H3B. Only one patient (Case 3) had a TERT promoter mutation (C228T).

Treatment outcome of brainstem glioma with IDH mutation

Three of four patients with IDH-mutant brainstem glioma showed recurrence during the observation period. All recurrences were observed within the radiation field as a gross tumor volume. No radiation-induced brain injury was observed. The median PFS for all four IDH-mutant patients was 68.4 months; there was a statistically significant difference between the IDH-mut group and the IDH-WT group (5.6 months, $p = 0.0139$) (Fig. 1a).

Until the last follow-up, three of four patients had died. Their median OS was 85.2 months (range 28.4–123.2 months). Kaplan–Meier analyses demonstrated that the IDH-mut group was associated with a longer OS than the IDH-WT group (12.0 months, $p = 0.0140$), despite similar localization (Fig. 1b). No significant difference was noted in PFS and OS of IDH-WT group according to H3K27M mutations (Supplementary Fig. 1).

Radiological findings of brainstem glioma with IDH mutation

All patients in the IDH-mut group exhibited hypo-intensity or iso-intensity upon T1-weighted imaging (WI), and hyperintensity upon fluid-attenuated inversion recovery. Enhanced lesions on gadolinium-enhanced (Gd-) T1-weighted imaging (WI) were not observed in two patients, although they were seen in the other two. In the IDH-WT group, six patients had enhanced lesions while one did not. The percentage of patients with contrast-enhanced lesions was 50% in the IDH-mut group and 85.7% in the IDH-WT group.

Case presentation

Case 1

The 32-year-old male presented a one-year of left-sided facial tightness and headache. MRI revealed swelling and distinctive abnormal signals within the brainstem, involving the pons to the medulla and left middle cerebellar peduncle (Fig. 2a–c). Despite two surgical biopsies, biopsy specimens revealed a small amount of astrocytic lesions, rendering definitive diagnosis challenging (Fig. 2d). The tumor grew and symptoms such as diplopia, left facial palsy, and ataxia appeared. Glioma was diagnosed based on imaging findings and clinical course without resorting to pathological findings. The patient received radiation therapy (54Gy/27Fr). 29 months post-treatment initiation, localized relapse occurred. Subsequently, TMZ (150－200 mg/m^2, day 1－5, every 4 weeks) and Bev were introduced; however, the patient succumbed to the disease at 47.1 months from the initial biopsy. Additional genetic analysis confirmed an IDH1 R132H mutation, and wild-type H3F3A and HIST1H3B. MLPA method indicated no co-deletion in 1p19q and no deletion in CDKN2A/B. Retrospectively, according to the WHO 2021 criteria, the integrated diagnosis was concluded as astrocytoma, IDH-mutant, CNS WHO grade 3.

Case 2

The 21-year-old male presented a one-year history of left-sided deafness and two episodes of paralysis in the right upper extremity. MRI revealed swelling and distinctive abnormal signals within the brainstem, spanning from the pons to the left middle cerebellar peduncle, primarily concentrated in the cerebellar peduncle (Fig. 3a–c). A craniotomy (biopsy) was conducted, unveiling histological findings of a dense localized population of atypical astrocytic glial cells, devoid of palisading necrosis and microvascular proliferation (Fig. 3d). Immunostaining displayed positivity for GFAP, Olig2, and p53, but negativity for IDH1-R132H. Genetic analysis confirmed an IDH2 R172G mutation, and wild-type H3F3A and HIST1H3B. MLPA method indicated no co-deletion in 1p19q and no deletion in CDKN2A/B. At this point, the diagnosis was anaplastic astrocytoma, IDH-mutant. The patient was administered TMZ (75 mg/m^2), followed by 54 Gy of radiation therapy, and subsequently a continuous TMZ administration (150－200 mg/m^2, day 1–5, every 4 weeks) totaling 24 courses. There has been no recurrence to date, after five years since the initial surgery (Fig. 3e). Retrospectively, according to the WHO 2021 criteria, the integrated diagnosis was concluded as astrocytoma, IDH-mutant, CNS WHO grade 3.

Case 3

The patient was a 35-year-old male who gradually manifested left facial palsy, hoarseness, diplopia, dysphagia, and left-ear hearing loss over 4 years. MRI revealed pronounced swelling and anomalous signals within the brainstem, spanning from the pons to the medulla (Fig. 4a–c). Glioma was diagnosed based on imaging findings without resorting to biopsy. Treatment involved TMZ (75 mg/m^2) combined with radiation (54 Gy/27 Fr). Additionally, 24 courses of maintenance therapy with TMZ (150－200 mg/m^2, day 1－5, every 4 weeks) were administered, after which the tumor decreased in size. One month after completion of TMZ maintenance chemotherapy, localized relapse occurred. Subsequently, Bev was introduced; however, the patient succumbed to the disease at 28.4 months from diagnosis. Autopsy facilitated tissue diagnosis and genetic analysis. Histological examination unveiled a dense localized population of atypical astrocytic glial cells, minigemistocytes, and palisading necrosis, without indications of microvascular proliferation (Fig. 4d). Immunostaining displayed positivity for GFAP, Olig2, p53, and IDH1 R132H. Genetic analysis confirmed an IDH1 R132H mutation, a TERT promoter mutation (C228T), and the wild-type status of H3F3A and HIST1H3B. MLPA analysis revealed no co-deletion in 1p19q and no deletion in CDKN2A/B. The integrated diagnosis was concluded as astrocytoma, IDH-mutant, CNS WHO grade 4.

Case 4

The 36-year-old male presented a one-month history of headache and diplopia. MRI revealed pronounced swelling and anomalous signals within the brainstem, involving the pons to the right middle cerebellar peduncle (Fig. 5a–c). Brainstem glioma was diagnosed based on imaging findings without resorting to biopsy. Treatment involved TMZ (75 mg/m^2) combined with radiation (54 Gy/27 Fr). Additionally, 24 courses of maintenance therapy with TMZ (150－200 mg/m^2, day 1－5, every 4 weeks) were administered, after which the tumor decreased in size (Fig. 5d). Six years post-treatment initiation, localized relapse occurred in the brainstem (Fig. 5e). Subsequently, rechallenge with TMZ therapy (200 mg/m^2, day 1－5, every 4 weeks) was administered. Although the recurrence tumor was decreasing in size temporally by TMZ, a re-growing tumor was observed in the right cerebellar hemisphere on the 16th course. A craniotomy (removal) for cerebellar lesion was conducted, unveiling histological findings of small, immature morphology of tumor cells with proliferation, extensive infiltration, and microvascular proliferation (Fig. 5f). Immunostaining displayed positivity for p53 and IDH1-R132H, but negativity for H3K27M. IDH1 R-132H mutation was confirmed by a next-generation sequencing-based comprehensive cancer genome profiling test. The diagnosis was astrocytoma, IDH-

mutant, CNS WHO grade 4. TMZ and Bev were not effective thereafter, the patient succumbed to the disease at 123.2 months from diagnosis.

Discussion

Brainstem gliomas tend to be more prevalent in children and are associated with an extremely bleak prognosis. Not only is the occurrence of brainstem gliomas in adults less frequent than in children, but the outcome is also comparatively better than in children (median OS 19.5 months vs. 9－11 months) [36,39], which is attributable to the differences in the molecular profiles. While 71－78% of pediatric brainstem glioma cases exhibit H3K27M mutations [21,41], only 37.2% of adult brainstem glioma cases have H3K27M mutations, and 34% harbor IDH1/2 mutations [39]. In the cases biopsied in this study, 33% were IDH-mutant gliomas, 33% were DMGs, and 25% were H3-wildtype/IDH-wildtype. Adult brainstem gliomas represent a heterogeneous disease group. Notably, a previous report had indicated the presence of H3K27M mutations or IDH mutations in adult infratentorial gliomas portending different prognoses, with median OS durations of 13 months and 43.5 months, respectively [5]. Our results also indicated the median OS of the IDH-mut group to be 85.2 months, predominantly longer than the 12.0 months observed in the IDH-WT group including H3K27-mutant DMGs. Based on the results, IDH-mutant was concluded to be a good prognostic subtype in adult brainstem gliomas. Genetic testing following tissue collection is currently essential for the diagnosis of IDH-mutants. There is no report summarizing the imaging findings for

IDH-mutant brainstem gliomas in adults. In addition to this study, previous reports in which MRI findings were specified have been summarized in Table 3 [8,12,18,28]. Contrast-enhanced lesions in IDH-mutant brainstem gliomas were found in 7 of the 16 cases (43.8%). However, in this study, contrast lesions were observed in 85.7% of the IDH-WT group. Schulte et al. analyzed 60 adult H3K27 mutant DMGs and reported enhanced lesions in 79% of them [34]. Qi et al. reported that, in general, a large proportion of IDH-mutant gliomas do not have contrast-enhancing lesions [31]. Therefore, genetic analysis by biopsy may be more useful in adults with brainstem glioma without contrast-enhancing lesions than with contrast-enhancing lesions.

The prognosis of IDH-mutant brainstem glioma in adults has been discussed from two perspectives, as follows:

(1) Recent studies have proposed that non-IDH1-R132H mutations, accounting for only 10–18% of IDH mutations in adult supratentorial gliomas, constitute a significant portion (76%) in adult brainstem gliomas [5,32]. In our cases, three infratentorial astrocytomas (75%) exhibited the IDH1 R132H mutation, and one (25%) displayed the IDH2 R172G mutation. Although the frequency did not align with prior reports, it surpassed past reports of supratentorial gliomas. The IDH variant had previously been reported to not correlate with prognosis [5], and the trend corroborated in this case series.

(2) Radiation therapy is the only evidence-based treatment for DIPG that improves OS [23,38]. While the efficacy of chemotherapy for brainstem gliomas, including temozolomide, remains unverified [3,9], it is widely used nevertheless [33]. No prognostic benefit with temozolomide was reported in adults with H3K27M-altered DMG [6]. In IDH-mutant astrocytoma, temozolomide has been shown to improve prognosis [35]. Thus, even in brainstem gliomas, temozolomide can be expected to improve prognosis in IDH-mutant cases, which may be one reason why the IDH group has a better prognosis in our series. Further, there may be challenges due to temozolomide. Based on the latest WHO classification revised in 2021, two cases discussed above were designated as "Astrocytoma, IDH-mutant, WHO grade 4" after the relapse. Malignant histopathological findings in recurrent tumors might stem from malignant transformation against a background of temozolomide-induced hypermutation. In low-grade IDH-mutant astrocytoma, 37.5% of patients underwent grade 4 malignant transformation while 33.3% experienced hypermutation [43]. Given the risk of hypermutation, whether the use of early-stage temozolomide could truly contribute to improved prognosis in patients with an expected prolonged survival would require elucidation in further cases.

Recently, as first-line treatment for grade 2 gliomas with IDH1/2 mutations, the IDH inhibitor, vorasidenib, was shown to significantly prolong PFS over placebo [27]. In

the future, substituting IDH inhibitors for temozolomide in this disease group might mitigate the risk of hypermutation and improve prognosis. Consequently, genetic analysis from tissue samples advocates for proactive tissue collection whenever feasible.

This retrospective analysis has limitations including a small sample size and single-center study. Larger cohorts would be necessary to elucidate the clinical features of adult patients with IDH-mutant diffuse brainstem gliomas. Additionally, there may be selection bias in defining cohorts by tumors for which pathology and genetic information can be confirmed by surgical biopsy or resection. Thus, cases with IDH mutations may be included among cases that have not been biopsied or resected. Prospective trials would be needed to show the implication of our result.

In summary, IDH-mutant astrocytomas located in the brainstem form a discrete subtype within the spectrum of brainstem gliomas encountered in adults. Their presence and specific features and attributes are identified in the diagnostic workflow. Given the increasing importance of gene-based diagnosis, biopsy may be considered more aggressively in these cases, especially for lesions without contrast effects.

Statements and Declarations

Conflicts of interest: The authors declare they have no conflict of interest.

Availability of data and material: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Code availability: Not applicable.

Ethical standards: All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent to participate: Since the study was retrospective, the requirement for informed consent was waived.

Consent for publication: The authors declare their consent for publication.

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Author contributions

Conception and design: Oki, Yamaguchi. Acquisition of data: Oki, Ishi, Sawaya, Okamoto, Tanei, Okada, Yamaguchi. Analysis and interpretation of data: Oki, Ishi, Tanei, Tsuda, Tanaka. Drafting the article: Oki. Critically revising the article: Ishi, Nishioka, Okada, Yamaguchi. Approved the final version of the manuscript on behalf of all authors:

Yamaguchi. Statistical analysis: Oki. Administrative/technical/material support: Motegi, Tanaei, Tsuda, Mori, Nishioka, Okada, Aoyama, Tanaka. Study supervision: Fujimura.

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Figure legends

Fig. 1 Kaplan－Meier survival curve for adult brainstem gliomas in this study. (a) Progression-free survival of the IDH-mut group was significantly longer than the IDH-WT group (p = 0.0139). (b) Overall survival of the IDH-mut group was significantly longer than IDH-WT group (p = 0.0140)

Fig. 2 Radiological and pathological findings of case 1. (a) Fluid attenuated inversion recovery showed hyper-intense mass in pons. (b) The lesions extended from the pons to the medulla. (c) Gadolinium-enhanced T1-weighted imaging showed no enhanced lesion. (d) Hematoxylin and eosin stain showed a small amount of low-cellular lesions with mildly increased astrocytic cells harboring various sizes of oval to elongated nuclei in the cerebellum; that was indefinite for neoplasia on histology (200×)

Fig. 3 Radiological and pathological findings of case 2. (a,b) Fluid attenuated inversion recovery (FLAIR) showed hyper-intense mass in pons extending to the left middle cerebellar peduncle. (c) Gadolinium-enhanced T1-weighted imaging showed heterogeneous enhanced lesion (d) Hematoxylin and eosin stain showed a dense regional atypical astrocytic glial cell population, and no evidence of palisading necrosis and microvascular proliferation (400×). (e) FLAIR imaging showed no evidence of regrowth after chemoradiotherapy

Fig. 4 Radiological and pathological findings of case 3. (a) Fluid attenuated inversion recovery showed hyper-intense mass in pons. (b) The lesions extended from the pons to the medulla in two cases. (c) Gadolinium-enhanced T1-weighted imaging showed that two cases had no enhanced lesion. (d) Hematoxylin and eosin stain showed a dense regional atypical astrocytic glial cell population and palisading necrosis, and no evidence of microvascular proliferation (100×)

Fig. 5 Radiological and pathological findings of case 4. (a,b) Fluid attenuated inversion recovery (FLAIR) showed hyper-intense mass in pons extending to the right middle cerebellar peduncle. (c) Gadolinium-enhanced T1-weighted imaging showed faint enhanced lesion. (d) FLAIR showed the tumor decreased in size after 24 course of maintenance therapy with TMZ. (e) FLAIR showed localized relapse occurred in the brainstem and right middle cerebellar peduncle six years after initial treatment. (f) Hematoxylin and eosin stain showed hyperchromatic undifferentiated tumor cells with microvascular proliferation (200x)

Supplementary Fig. 1 Kaplan－Meier survival curve for adult brainstem gliomas in IDH-WT group. (a) There was no difference in Progression-free survival between H3K27M(+) and H3K27M(-). (b) There was no difference in Overall survival between H3K27M(+) and H3K27M(-).

Table 1 Patient, tumor and treatreatment characteristics of adult IDH-mutant brainstem glioma

Case No.	Age/sex	Primary lesion	Primary lesion (detail)	Tissue sampling method	Chemotherapy	Radiotherapy	Pretreatment KPS	1 month posttreatment KPS
1	32/M	brainstem	pons-medulla	needle biopsy	TMZ, Bev	54Gy/27Fr	80	80
2	21/M	brainstem	pons-cerebellar peduncle	open biopsy	TMZ	54Gy/27Fr	90	90
3	35/M	brainstem	pons-medulla	autopsy	TMZ, Bev	54Gy/27Fr	80	70
4	36/M	brainstem	pons-medulla	open biopsy (at recurrence)	TMZ, Bez	54Gy/27Fr	90	90

KPS: karnofsky performance status, TMZ: temozolomide, Bev: Bevacizumab, Gy: gray, Fr: fractions

Table 2 Clinical outcomes and genentic features of adult IDH-mutant brainstem glioma

case No.	Integrated diagnosis	recurrence	PFS (months)	OS (months)	Status	IDH mutation type	ATRX loss	TP53 mutation	CDKN2A/B homodeletion	1p19q codeletion	TERT promoter status	H3F3A	HIST 1H3B
1	Astrocytoma, IDH-mutant, CNS WHO grade 2	+	35.8	47.1	dead	IDH1 R132H	NA	-	-	-	wild	wild	wild
2	Astrocytoma, IDH-mutant, CNS WHO grade 3	-	-	63.9	alive	IDH2 R172G	NA	+	-	-	wild	wild	wild
3	Astrocytoma, IDH-mutant, CNS WHO grade 4 (at autopsy)	+	26.5	28.4	dead	IDH1 R132H	+	+	-	-	mutation (C228T)	wild	wild
4	Astrocytoma, IDH-mutant, CNS WHO grade 4 (at recurrence)	+	101.1	123.2	dead	IDH1 R132H	+	+	+	NA	wild	wild	wild

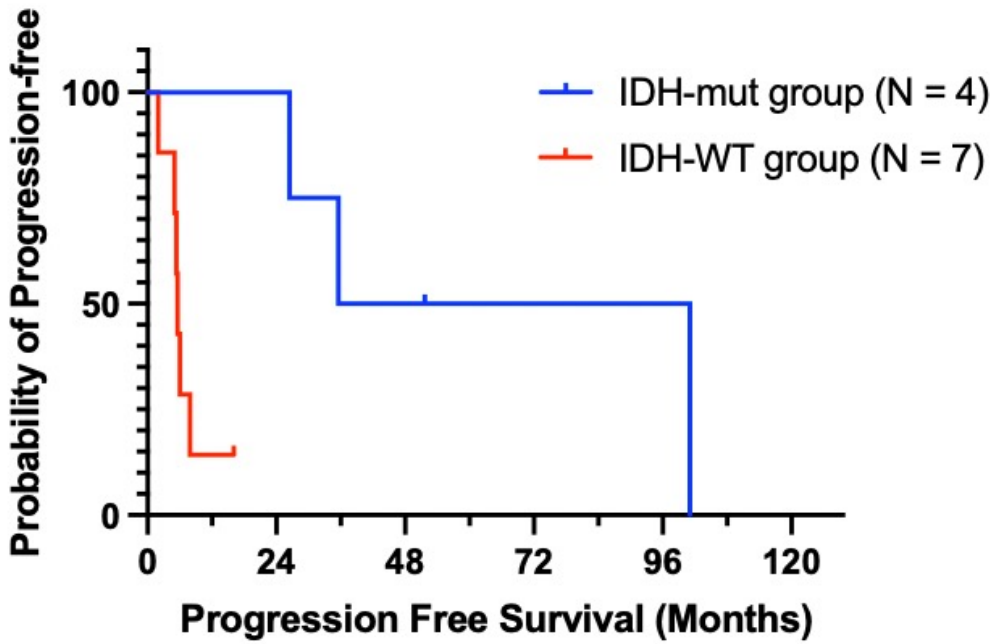
PFS: progression free survival, OS: overall survival, IDH: isocitrate dehydrogenase, ATRX: alpha thalassemia/mental retardation syndrome X-linked, TP53: tumor protein p53, CDKN2A/B: cyclin-dependent kinase inhibitor 2A/B, TERT: telomerase reverse transcriptase, CNS: central nervous system, WHO: world health organization, NA: not appricable, +: present, -: not present

Table 3 Previous reports of adult IDH-mutant brainstem glioma

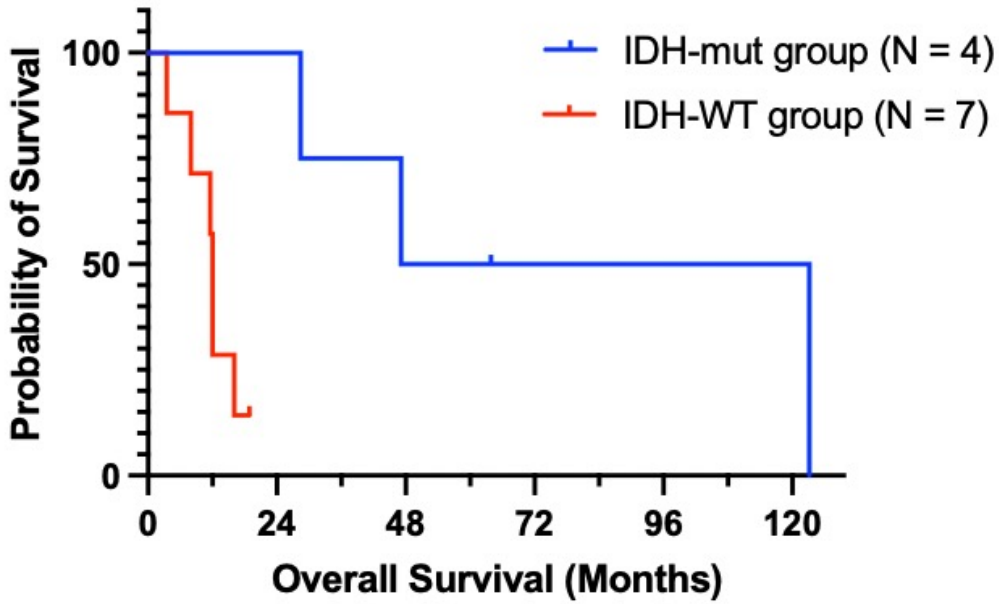
Author	Age	Sex	contrast enhancement	IDH mutation type	Integrated diagnosis (or Histologic diagnosis)	OS (months)	Status
this study	33	Male	-	IDH1 R132H	Astrocytoma, IDH-mutant, WHO grade 2	47.1	dead
	21	Male	+ (heterogeneous)	IDH2 R172G	Astrocytoma, IDH-mutant, WHO grade 3	57.8	alive
	35	Male	-	IDH1 R132H	Astrocytoma, IDH-mutant, WHO grade 4	28.5	dead
	36	Male	+ (faint patcy)	IDH1 R132H	Astrocytoma, IDH-mutant, WHO grade 4	121.1	dead
Iwahashi et al. (2023)	27	Male	-	IDH1 R132G	Astrocytoma, IDH-mutant, WHO grade 2	63	dead
	24	Male	-	IDH1 R132S	Astrocytoma, IDH-mutant, WHO grade 2	64	alive
	33	Female	-	IDH1 R132H	Astrocytoma, IDH-mutant, WHO grade 2	26	alive
	38	Male	-	IDH1 R132S	Astrocytoma, IDH-mutant, WHO grade 2	201	alive
Nagase et al. (2023)	23	Female	-	IDH1 R132H	Astrocytoma, IDH-mutant, WHO grade 2	12	alive
Chang et al. (2021)	19	Female	-	IDH1 R132S	Astrocytoma, IDH-mutant, WHO grade 3	62	dead
	17	Male	-	IDH1 R132H	Astrocytoma, IDH-mutant, WHO grade 2	36	alive
	24	Male	+ (small area)	IDH1 R132H	Astrocytoma, IDH-mutant, WHO grade 2	18	alive
Eschbacher et al. (2021)	37	Male	+	IDH1 R132C	Anaplastic astrocytoma, IDH-mutant	111.7	dead
	34	Female	+	IDH1 R132S	Anaplastic astrocytoma, IDH-mutant	4.8	dead
	53	Male	+	IDH1 R132H	Anaplastic astrocytoma, IDH-mutant	14.2	dead
	50	Male	+	IDH1 R132H	Anaplastic astrocytoma, IDH-mutant	28.6	dead

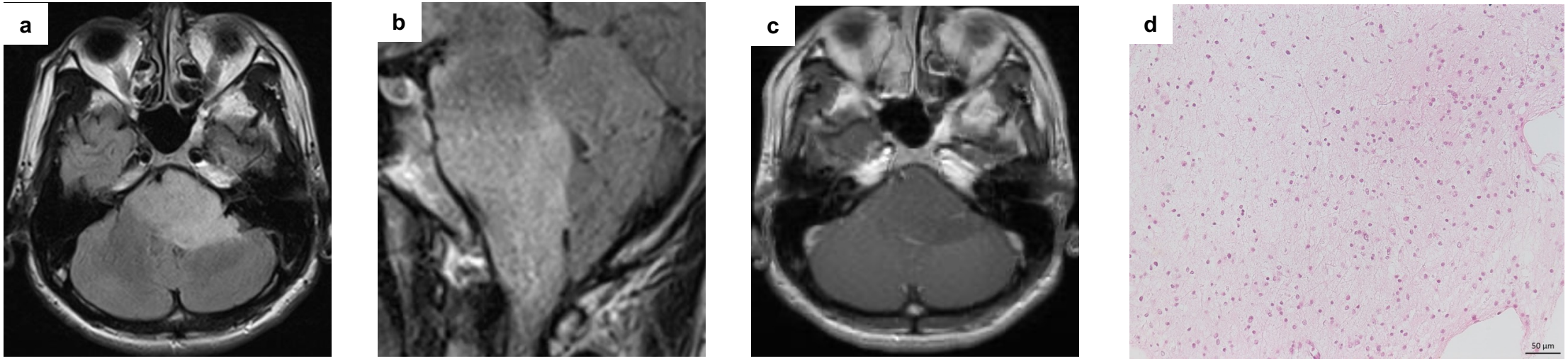
OS: overall survival, IDH: isocitrate dehydrogenase, WHO: world health organization, NA: not appricable, +: present, -: not present

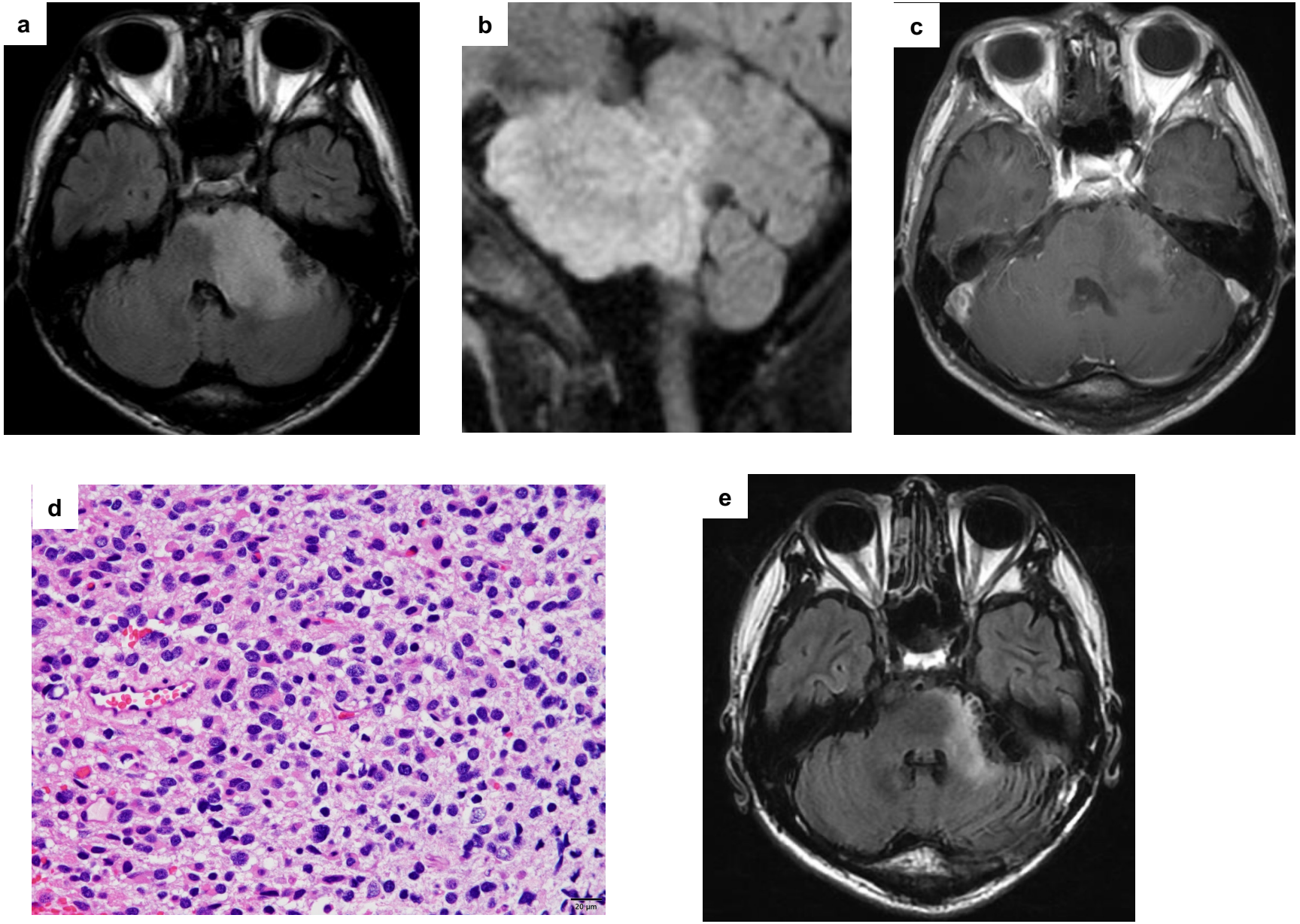
a

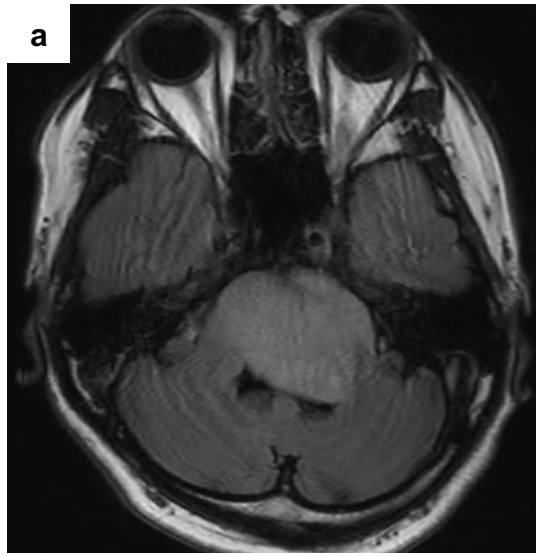

Probability of Progression-free
100
50
0
0
24
48
72
96
120
Progression Free Survival (Months)
IDH-mut group (N = 4)
IDH-WT group (N = 7)

b


Probability of Survival
100
50
0
0
24
48
72
96
120
Overall Survival (Months)
IDH-mut group (N = 4)
IDH-WT group (N = 7)


a
b
c
d
50 µm


a
b
c
d
20 µm
e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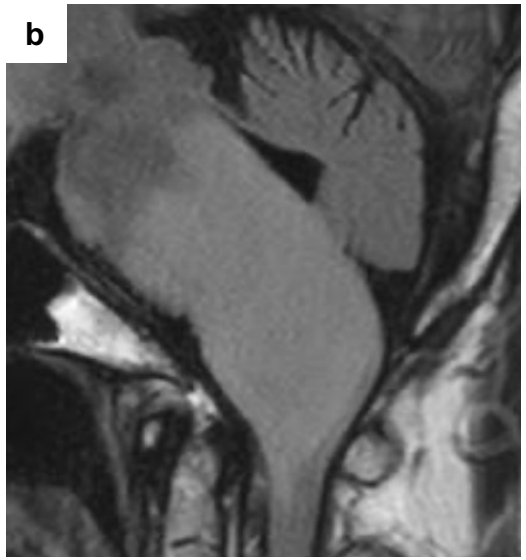
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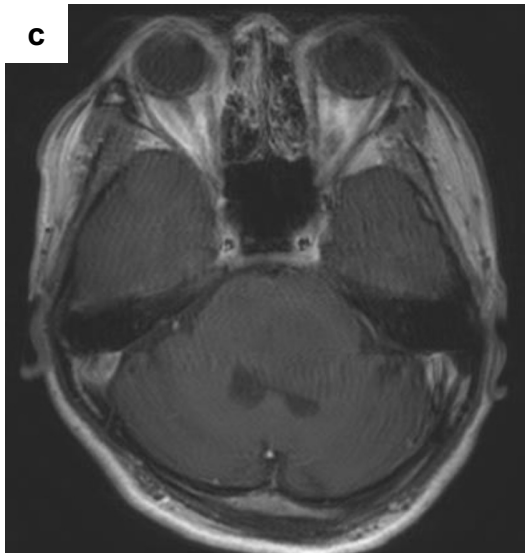
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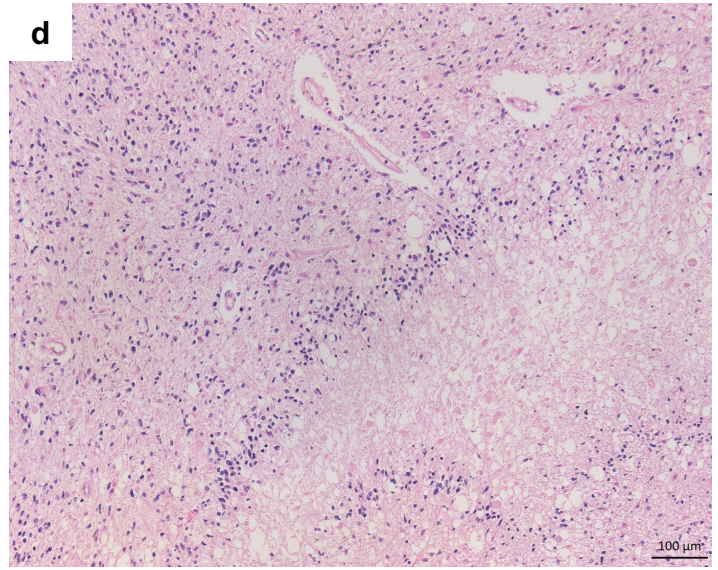
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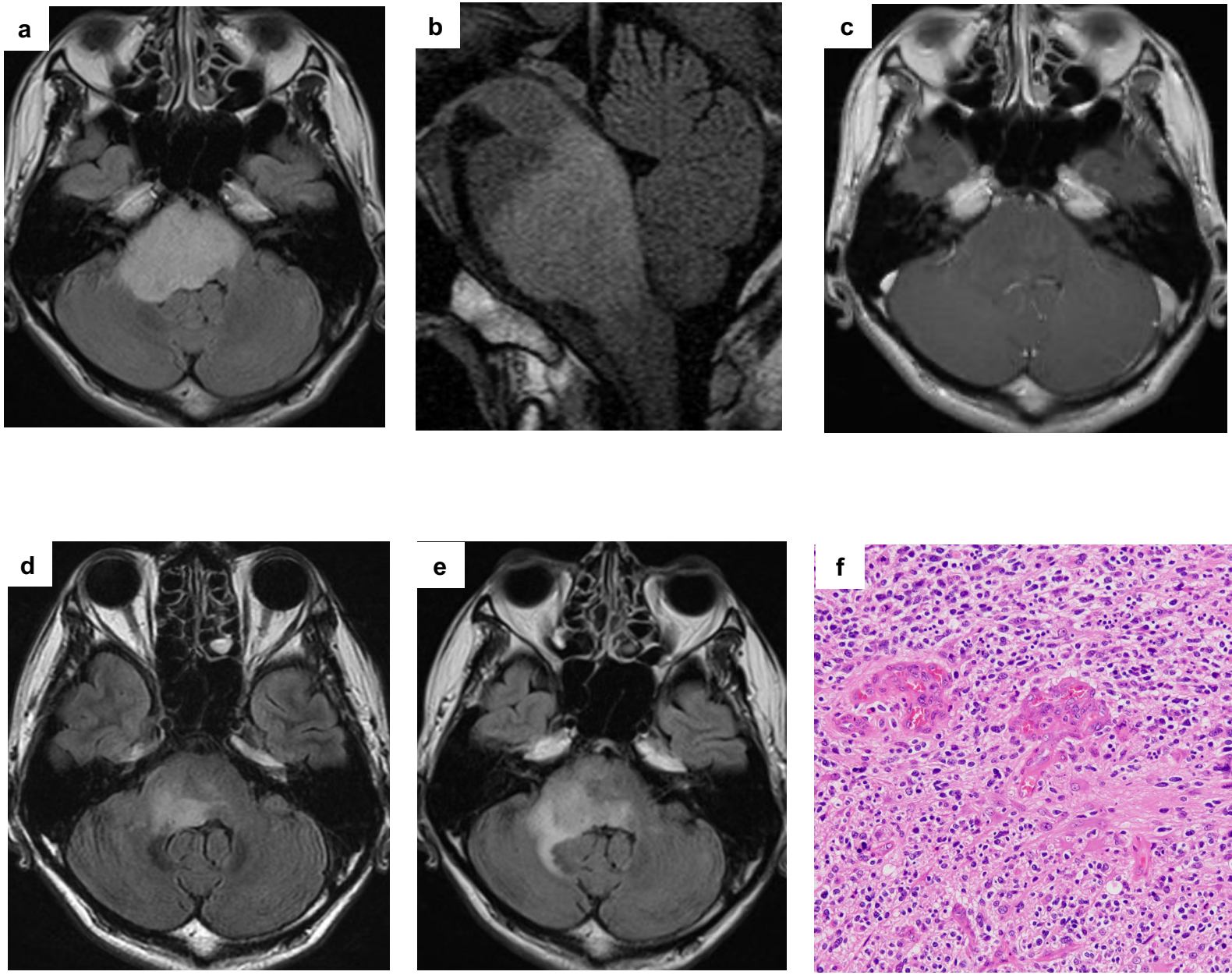
100 µm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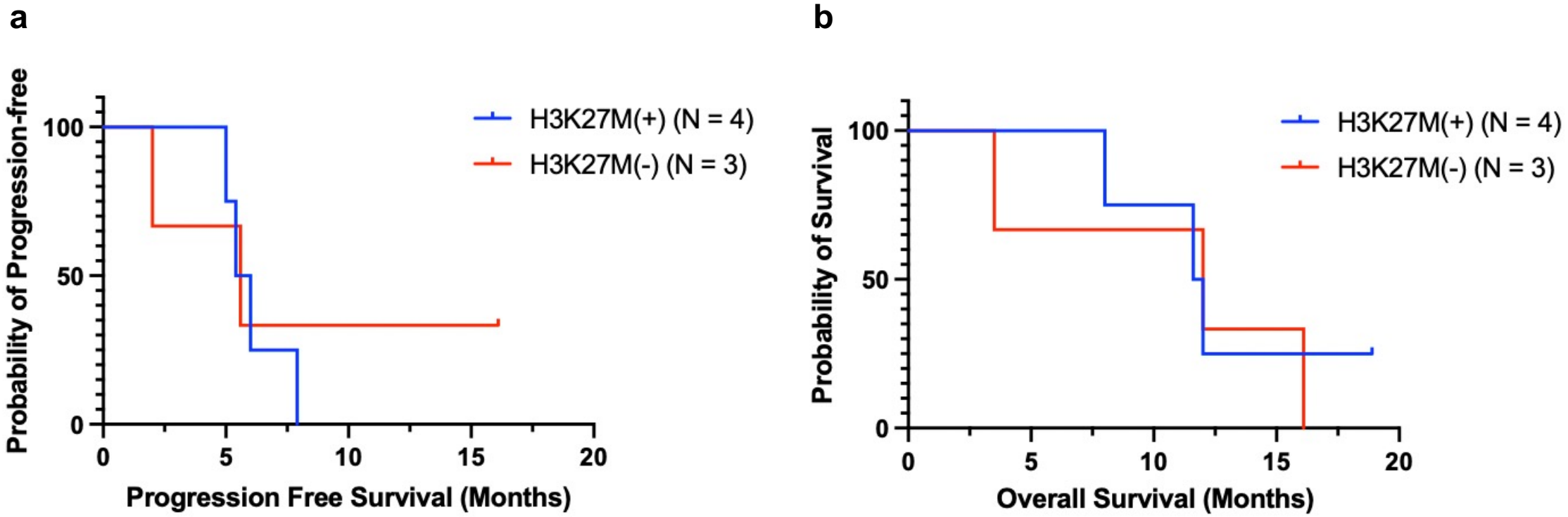
b
c
d
e
f
50 µm


a
Probability of Progression-free
100
50
0
0
5
10
15
20
Progression Free Survival (Months)
H3K27M(+) (N = 4)
H3K27M(-) (N = 3)
b
Probability of Survival
100
50
0
0
5
10
15
20
Overall Survival (Months)
H3K27M(+) (N = 4)
H3K27M(-) (N = 3)