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Malignant Progression of an IDH Mutant Brainstem Glioma in Adult

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Abstract

Brain stem gliomas (BSG) in adults are rare and less aggressive than those in children. However, the molecular profile of adult BSG cases has not been well characterized. We report a case of adult BSG with isocitrate dehydrogenase (IDH) mutation. A 43-year-old male was admitted to our hospital with diplopia and right-sided hypesthesia. An open biopsy led to the tumor being diagnosed as a diffuse astrocytoma. Immunohistochemically, the tumor was positive for IDH1 R132H, but negative for H3K27M. The patient received 54 Gy of local radiotherapy and adjuvant temozolomide, which resulted in the size of the lesion decreasing significantly. At 56 months after the initial diagnosis, the patient was referred to our hospital with a severe headache and ataxia. Magnetic resonance imaging (MRI) revealed a contrast-enhanced lesion in the brain stem, which extended into the left cerebellar hemisphere and brainstem. Partial tumor removal was performed, and a pathological examination revealed the features of glioblastoma. Immunohistochemically, the tumor was positive for IDH1 R132H and p53 and negative for ATRX. To the best of our knowledge, there are few reports about adult case of brain stem astrocytoma to be confirmed via histological and molecular examinations of the primary and recurrent tumor. We exhibit detailed pathological and molecular findings which resembles to IDH mutant supratentorial diffuse astrocytic tumors.

Keywords: brain stem glioma, adult, IDH mutation

Introduction

While diffuse intrinsic pontine glioma (DIPG) is a malignant brainstem tumor that affects children, brain stem gliomas (BSG) are rare in adults, and such cases are not well understood.[1)] In addition, a molecular analysis of a DIPG detected a pathognomonic point mutation in amino acid 27 (K27M) of the histone H3.3 gene (H3K27M); however, the molecular profile of adult BSG cases has not been well characterized.[2)]

Although isocitrate dehydrogenase 1 (*IDH1*) and *IDH2* are frequently mutated genes in many types of glioma, with incidences of up to 75% in grade II and grade III supratentorial gliomas,[3)] these mutations are rare in adult cases of BSG.[4)] Previous studies have reported that supratentorial diffuse astrocytomas with *IDH* mutations often recur and progress to glioblastoma.[1)] A small number of similar BSG cases have been reported, but their molecular biological characteristics were not elucidated.[5)]

Here, we report a case in which a BSG progressed to glioblastoma in an adult 56 months after the initial treatment.

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Case Presentation

A 43-year-old right-handed male was referred to our hospital with diplopia, which had been worsening for 24 months. Furthermore, he had suffered from right-sided sensory disturbance and left-sided facial paralysis for 6 months. Magnetic resonance imaging (MRI) revealed a high-intensity lesion, extending from the pons to the medulla, on T2-weighted (Fig. 1A). On contrast-enhanced T1-weighted imaging, no enhancement was seen (Fig. 1E). The symptoms were gradually progressive.

Adult brainstem tumors are relatively rare. Therefore, we have decided that treatment should be carried out after diagnosis confirmation by biopsy and pathological examinations. After informed consent was obtained from the patient, we performed an open biopsy of the brainstem lesion via a midline suboccipital approach. The tumor's histology was consistent with diffuse astrocytoma. After initial treatment with local radiotherapy (total dose: 54 Gy/30 fractions) and concurrent (75mg/m^2/day, 43 days) temozolomide-based chemotherapy, the tumor decreased in size slightly (Fig. 1B and 1F).

Pathological findings

A pathological examination involving hematoxylin and eosin (HE) staining showed moderate proliferation of atypical astrocytes (Fig. 2A). Immunohistochemically, the tumor cells were positive for glial fibrillary acidic protein (GFAP). The tumor cells were also immunopositive for H3K27me3 and IDH1 R132H and immunonegative for H3K27M (Fig. 2B–D). The Ki-67 labeling index was not determined due to the small size of the tissue specimen. As a result, the patient was diagnosed with diffuse astrocytoma, IDH mutant (based on the WHO 2016 classification of tumors of the central nervous system [CNS]).

Follow-up

The operation remained in biopsy, and the worsening of symptoms due to enlargement in the

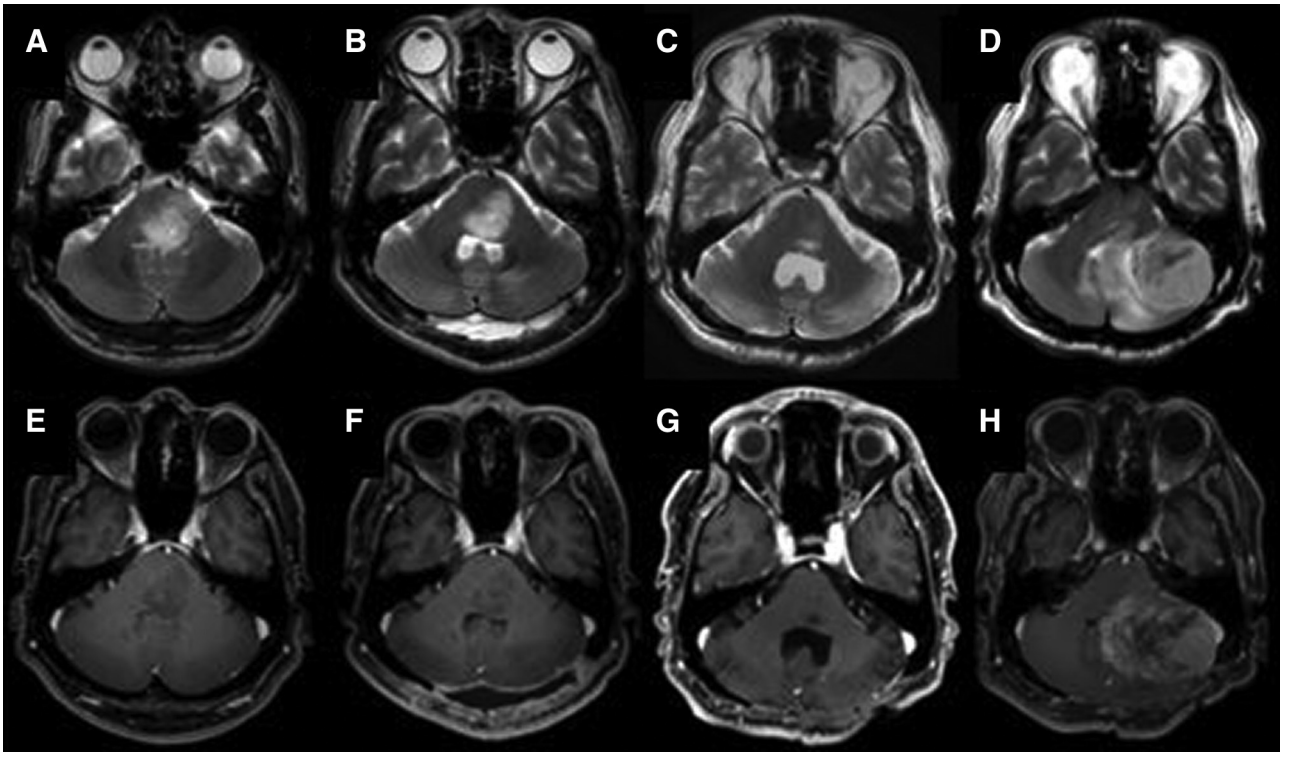

Fig. 1 T2-weighted MRI performed on admission showed a high-intensity area in the pontine lesion (A). Contrast-enhanced T1-weighted MRI revealed a hypointense lesion in the left pons, which did not exhibit enhancement (E). T2-weighted MRI (B) and contrast-enhanced T1-weighted MRI (F) performed after the initial treatment revealed that the size of the lesion had decreased slightly. T2-weighted (C) and contrast-enhanced T1-weighted (G) MRI performed at 48 months after the initial diagnosis showed that the high-intensity area in the pontine lesion had decreased in size. At this point, the 24 courses of adjuvant temozolomide had completed. T2-weighted (D) and contrast-enhanced T1-weighted (H) MRI performed at 57 months after the initial diagnosis revealed a large recurrent tumor in the pons and cerebellum. MRI: magnetic resonance imaging.

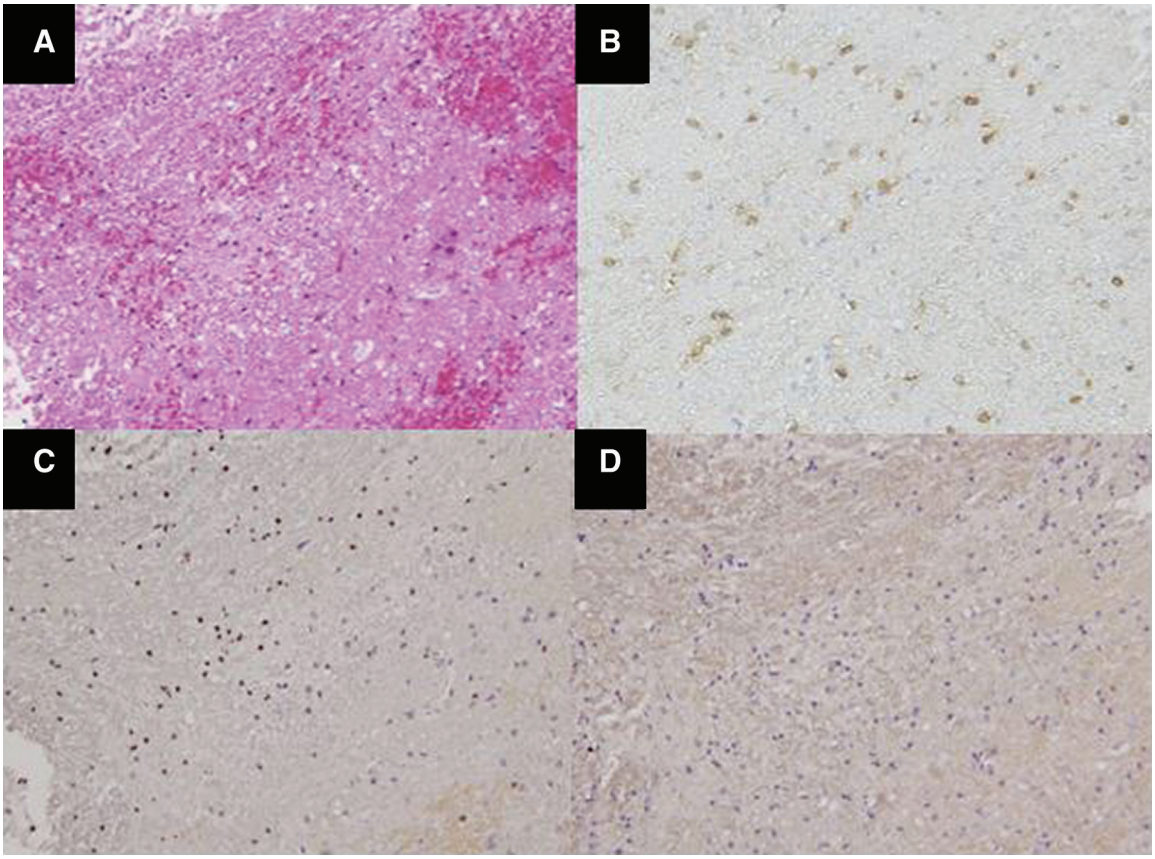

Fig. 2 A histological examination of the tumor involving hematoxylin and eosin staining demonstrated moderately increased cellularity and mild pleomorphism, and the absence of necrosis and microvascular proliferation (A, ×200). Immunohistochemical analysis showed that the tumor was positive for IDH1 R132H (B) and H3K27me3 (C) and negative for H3K27M (D).

remaining tumor was afraid. According to the course of treatment, the sensitivity of TMZ was considered good. Therefore, total of 24 cycles of adjuvant (150–200mg/m^2/day, 5 days every 4 weeks) temozolomide were administered, and the size of the tumor significantly decreased (Fig. 1C and 1G).

After the 24 cycles of adjuvant therapy with TMZ, at 56 months after the initial diagnosis, the patient was referred to our hospital with a severe headache and ataxia. Contrast-enhanced T1-weighted MRI detected a large tumor, extending from the pons to the left cerebellar hemisphere (Fig. 1D and 1H). The left cerebellar lesion was subtotally removed via left lateral suboccipital craniotomy and histologically diagnosed as a glioblastoma, IDH mutant. Postoperatively, the patient was treated with stereotactic radiotherapy (36 Gy/9 fractions) for the remnant contrast-enhanced lesion attached to brainstem. However, the lesion progressed with compression and invasion to the brainstem. The patient died due to uncontrollable local recurrence 3 months after progression.

Histological findings

A histological examination showed the dense proliferation of atypical astrocytes, necrosis, and vascular endothelial hyperplasia. Therefore, glioblastoma, WHO grade IV, was diagnosed, which disagreed with the initial pathological findings (Fig. 3A). The tumor cells were immunopositive for IDH1 R132H, H3K27me3, and p53 and immunonegative for H3K27M and the transcriptional regulator ATRX (Fig. 3B–3F). We also evaluated the mismatch repair proteins that reported to cause inactivating mutations in the treatment with temozolomide.[6,7] The tumor cells were immunonegative for MSH2 and MSH6 (Fig. 3G–3J).

Molecular analysis

Genomic DNA was extracted with the QIAamp DNA mini kit (Qiagen), according to the manufacturer's protocol. The mutational status of the *IDH1/2, H3F3A*, and *HIST1H3B* genes and the *TERT* promoter were analyzed using Sanger sequencing, as described previously.[8] The copy number statuses of 1p and 19q were examined by multiplex ligation-dependent

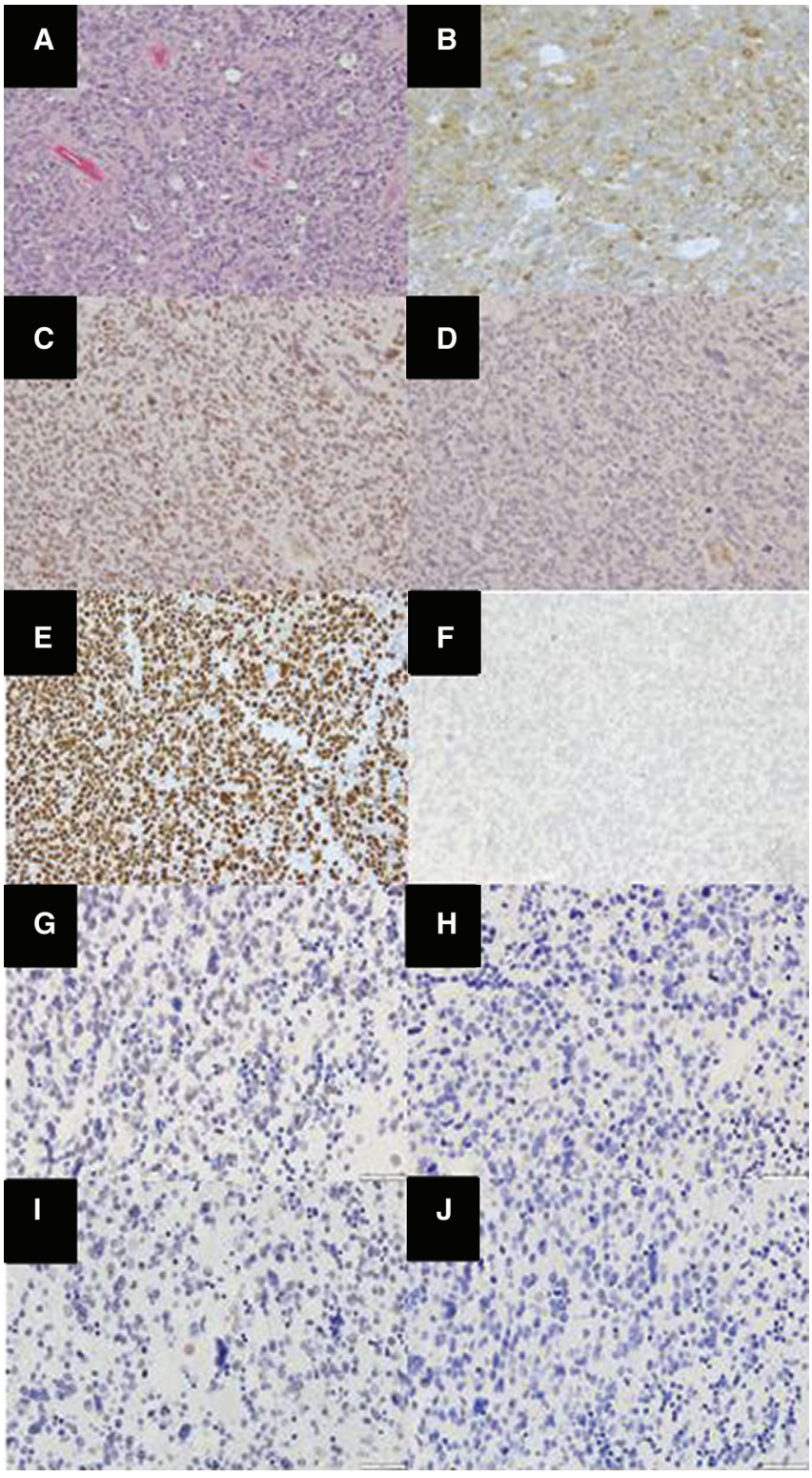

Fig. 3 A histological examination of the cerebellar recurrent tumor involving hematoxylin and eosin staining revealed high cellularity, mitosis, microvascular proliferation, and necrosis (A, ×200). Immunohistochemical analyses of IDH1 R132H (B), H3K27me3 (C), H3K27M (D), p53 (E), and ATRX (F) expression were performed. The tumor cells were positive for IDH1 R132H (B), H3K27me3 (C), and p53 (E) and negative for H3K27M (D). The loss of nuclear ATRX expression was observed (F). Additionally, the tumor cells were immunopositive for MLH1 (G) and PMS2 (I), immunonegative for MSH2 (H) and MSH6 (J).

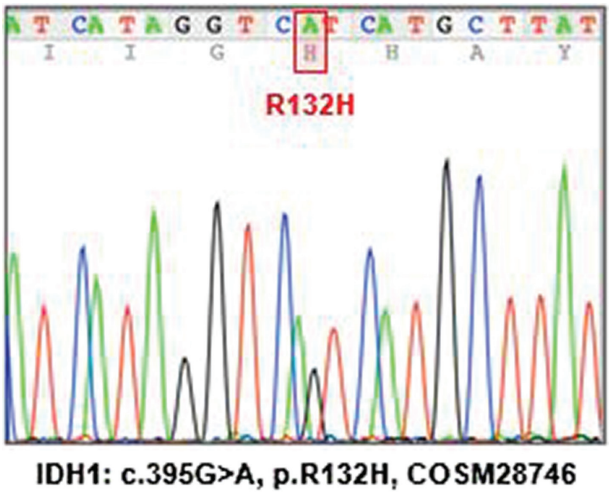

Fig. 4 DNA sequencing of the *IDH1* gene. The *IDH1* R132H mutation was detected.

probe amplification (MLPA). Then, the copy number status of CDKN2A/B was also inspected in the same manner.[8] In the *MGMT* promoter methylation analysis, we performed quantitative methylation-specific polymerase chain reaction (PCR) after the bisulfite modification of tumor DNA.[9] Although the *IDH1* R132H mutation was detected, no other hotspot mutations were found (Fig. 4). There was a partial loss of copy number in 19q, and no alteration in CDKN2A/B. In addition, the promoter region of the *MGMT* gene was highly methylated.

Discussion

There is a lack of detailed information about the molecular genetic features of BSG in adults because of the shortage of specimens and the small number of reported cases. BSG account for 10% of brain tumors in children and about 2% of brain tumors in adults.[10] In childhood, these tumors carry the worst prognosis of any brain tumor, with a median survival of <1 year.[11] On the other hand, a review of the literature suggested that BSG are generally less aggressive in adults than in children.[2,5,12,13]

Previously, Guillamo et al. reviewed the cases of 48 adults with BSG, and their median overall survival and 3-year survival rate were 5.4 years and 66%, respectively.[5] The latter study proposed three main groups of BSG, according to their histological, clinical, and MRI findings: (1) Adult diffuse intrinsic low-grade brainstem gliomas; (2) adult malignant brainstem gliomas; and (3) focal tectal brainstem gliomas, which are benign tumors. The group 1 tumors were the most common BSG and accounted for 46% of cases. These tumors occurred in young adults (<40 years old), and on MRI they appeared as infiltrative diffuse pontomedullary tumors without necrosis and exhibited contrast enhancement. Although radiotherapy significantly improved survival in this group, suspected anaplastic transformation, which was characterized by contrast enhancement appearing after a long period of stable disease, occurred in 27% of cases. The overall median survival time of this group was 7.3 years. Although no molecular information was provided in this paper, adult diffuse intrinsic low-grade BSG exhibited favorable prognoses; however, they often displayed anaplastic changes at recurrence.

The characteristics of adult *H3K27M*-positive gliomas are similar to those reported in the pediatric population.[14–17] In the 2016 WHO classification of tumors of the CNS,[1] these tumors were classified under the heading "diffuse midline glioma, *H3K27M* mutant, WHO grade IV." Up to 90% of pediatric DIPG harbor a pathognomonic point mutation in the H3.3 gene *H3F3A* (~65% of cases) or the H3.1 gene *HIST1H3B* (~25% of cases).[14,15,18] On the other hand, Daoud et al.[19] reported that 7 of 25 (28%) adult BSG were positive for the *H3K27M* mutation, and the overall survival of the *H3K27M* mutation-positive cases was shorter than that of the wild-type *H3F3A* group.

IDH1 and *IDH2* gene mutations are observed at a frequency of 6–8% in infratentorial diffusely infiltrating gliomas.[4,20] Previous studies have reported that both *IDH* mutations and the *H3K27M* mutation are commonly associated with p53 overexpression, although these mutations are mutually exclusive.[16,17,21–23] In other studies, immunohistochemistry and/or Sanger sequencing indicated that 18–24% of adult BSG are positive for *IDH* mutations.[24,25] In addition, Zhang et al. reported that all eight of the *IDH* mutant BSG they examined also had *TP53* mutations and exhibited the hypermethylated phenotype.[25] Therefore, genetically, adult BSG with *IDH* mutations resemble typical *IDH* mutant supratentorial diffuse astrocytomas.[25] The median survival time of patients with *H3K27M* mutant BSG was 9 months[19] while the mean recurrence-free survival time of patients with *IDH* mutant BSG was 3 years.[26] It is suggested that patients with *IDH* mutations have a relatively good prognosis and exhibit good responses to chemotherapy and radiotherapy.[27]

Our case involved an adult diffuse intrinsic low-grade brainstem glioma (group 1) according to the classification reported by Guillamo et al..[5] Molecular and immunohistochemical analyses with recurrent tumor revealed the following profile: *IDH*-mutant, *H3F3A*-wild-type, p53-positive, and ATRX-negative, which were suggestive of a diagnosis of diffuse

astrocytoma, *IDH* mutant. The progression-free survival and overall survival of our patient were 56 months and 59 months, respectively. Although temozolomide was reported to be ineffective against *H3K27M* mutant DIPG, it could be effective against adult diffuse pontine gliomas with *IDH* mutations and methylated *MGMT* gene promoter regions.[28] However, this type of tumor can often progress to malignant glioma, as is seen in *IDH* mutant supratentorial diffuse astrocytomas. Additionally, our case showed abnormalities in mismatch repair proteins, such as MSH2 and MSH6 in recurrent tumor.[6,7] These abnormalities are reported to be caused in the treatment of GBM with temozolomide. Therefore, it is thought that there might be abnormalities of these proteins in the course and affect the progression.

There are some literatures report the characteristics of clinical course with molecular and genetic alterations in adult BSG.[29,30] Adult brainstem tumors are relatively rare cases, and confirmed diagnosis by detailed analysis might be useful for predicting prognosis.

Conclusion

In summary, we reported an adult case of *IDH* mutant diffuse pontine glioma, which progressed to glioblastoma and was histologically diagnosed based on detailed examinations of both primary and recurrent tumor samples. The tumor's pathological and molecular findings resembled those of *IDH* mutant supratentorial diffuse astrocytoma.

Since temozolomide might be an effective treatment for adult diffuse pontine gliomas, tumor sampling could be useful for obtaining a molecular diagnosis and determining the optimal treatment in adult cases of BSG.

Acknowledgments

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Conflicts of Interest Disclosure

The authors declare that they have no conflicts of interest.

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