

Adult isocitrate dehydrogenase–mutant brainstem glioma: illustrative case

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BACKGROUND Adult brainstem gliomas are rare entities that demonstrate heterogeneous biology and appear to be distinct from both their pediatric counterparts and adult supratentorial gliomas. Although the role of histone 3 mutations is being increasingly understood in this disease, the effect of isocitrate dehydrogenase (IDH) mutations remains unclear, largely because of limited data.

OBSERVATIONS The authors present the case of a 29-year-old male with an IDH1-mutant, World Health Organization grade III anaplastic astrocytoma in the dorsal medulla, and they provide a review of the available literature on adult IDH-mutant brainstem glioma. The authors have amassed a cohort of 15 such patients, 7 of whom have survival data available. Median survival is 56 months in this small cohort, which is similar to that for IDH wild-type adult brainstem gliomas.

LESSONS The authors' work reinforces previous literature suggesting that the role of IDH mutation in glioma differs between brainstem and supratentorial lesions. Therefore, the authors advocate that adult brainstem gliomas be studied in terms of major molecular subgroups (including IDH mutant) because these gliomas may exhibit fundamental differences from each other, from pediatric brainstem gliomas, and from adult supratentorial gliomas.

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KEYWORDS IDH; brainstem; glioma; molecular marker

Although brainstem gliomas have received considerable attention in the pediatric population, they represent only 1%–2% of gliomas in the adult population¹ and thus remain poorly understood. It is also becoming increasingly clear that the biological landscape of gliomas depends largely on patient age group (pediatric versus adolescent versus adult),² and thus each must be studied independently. Notably, brainstem gliomas portend a better prognosis (median survival 30–40 months) in the adult population than that of their supratentorial counterparts, but outcomes are highly variable and depend on the World Health Organization (WHO) grade.^{3,4}

Histone 3 mutations (most commonly H3K27M) are found in up to 80% of pediatric diffuse intrinsic pontine glioma (DIPG) cases and herald a universally poor prognosis in these patients.^{4,5} Despite these mutations initially being considered specific to the pediatric population, recent studies have demonstrated their presence in up to 30%–50% of adult brainstem gliomas, wherein they are also associated with a

significantly worse prognosis.^{6,7} Interestingly, on the one hand, outcomes in H3K27M-mutant midline gliomas have been reported as similar in pediatric and adult populations,⁸ suggesting overlapping biology in this subtype of tumor. Isocitrate dehydrogenase (IDH) mutations, on the other hand, are uncommon in brainstem gliomas and are more common in (but not exclusive to) the adult population.^{9,10}

Mutations in IDH, a rate-limiting enzyme in the Krebs cycle, are known to be associated with gliomagenesis.¹¹ A survey of The Cancer Genome Atlas cancer database reveals that 80% of adult nonbrainstem WHO grade II/III gliomas harbor this mutation,⁴ and in glioblastoma, it is associated with younger age, better prognosis, and secondary (rather than de novo) high-grade pathology.^{12,13} Recent evidence also suggests that IDH1-mutant low-grade gliomas may differ in their stem cell of origin compared with IDH1 wild-type counterparts,¹⁴ suggesting key differences in tumorigenesis.

ABBREVIATIONS DIPG = diffuse intrinsic pontine glioma; IDH = isocitrate dehydrogenase; MRI = magnetic resonance imaging; SD = standard deviation; WHO = World Health Organization.

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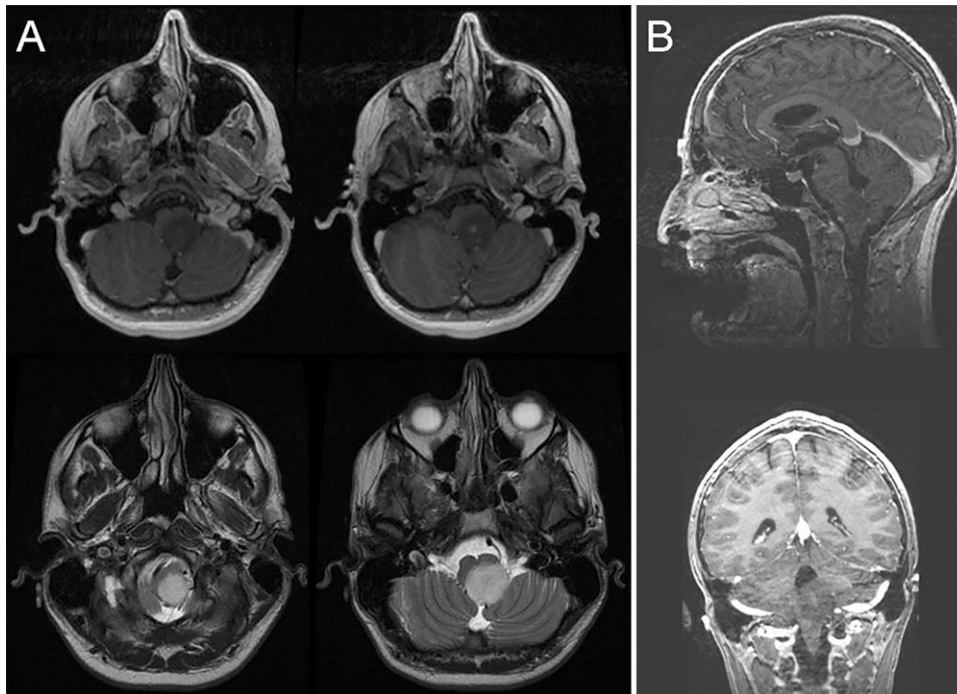


FIG. 1. Preoperative MRI. **A:** Axial cuts of dorsal medullary lesion. *Top row* is a T1-weighted sequence with gadolinium, demonstrating faint central contrast enhancement. *Bottom row* is a T2-weighted sequence. **B:** Sagittal (*top*) and coronal (*bottom*) T1-weighted sequence with contrast.

We present a case of an adult patient with IDH1-mutant brainstem anaplastic astrocytoma and provide a comprehensive review of the current literature on this poorly understood disease.

Illustrative Case

We present the case of a previously healthy 29-year-old male who developed hoarseness of voice in October 2019. He was subsequently diagnosed with vocal cord hemiparesis by an otolaryngology service at an outside institution, around which time he began to experience headaches, nausea, and vomiting. On neurological examination, he exhibited palatal and uvular deviation to the right, indicative of cranial nerve IX/X palsy, but he had no other cranial nerve or long-tract findings. Magnetic resonance imaging (MRI) revealed a mass with low T1 signal intensity and high T2 signal intensity centered within the left aspect of the dorsal medulla (Fig. 1). The lesion measured 21 mm anteroposterior × 24 mm transverse × 32 mm craniocaudal. There was faint central enhancement, no diffusion restriction, and no susceptibility artifact. The mass obstructed the left foramen of Luschka and foramen of Magendie and partially effaced the fourth ventricle.

The patient underwent a midline suboccipital craniotomy for biopsy of the lesion. After the dura overlying the medulla was opened, an area of clear discoloration with a lack of surface vascularity was identified that corresponded to the lesion according to the intraoperative neuronavigation (Fig. 2). The procedure was performed with neuromonitoring of cranial nerves IX–XII, including somatosensory evoked potentials and motor evoked potentials. Intraoperative brainstem stimulation and mapping were performed using a monopolar stimulation probe. No positive mapping was elicited within, above, or below the area of discoloration. A biopsy was performed from the area of interest, targeting the area of enhancement. There was

intraoperative confirmation of positive pathological tissue, consistent with a high-grade glioma. Postoperative MRI confirmed accurate sampling of the enhanced region of the tumor.

Histopathological analysis revealed a WHO grade III anaplastic astrocytoma. Interestingly, molecular studies revealed an IDH1 mutation (R132H via immunohistochemistry [IHC]; Fig. 3) and ATRX loss. Additionally, TP53 was mutated, and there were no BRAF V600E or H3K27M mutations. After review at the multidisciplinary tumor board,

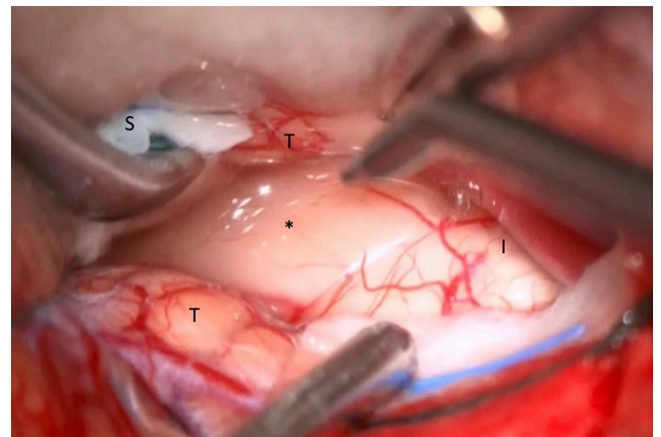


FIG. 2. Intraoperative view. Midline suboccipital craniotomy with view of the pial surface of the lesion (*) under the operating microscope. I = inferior; S = superior; T = tonsils.

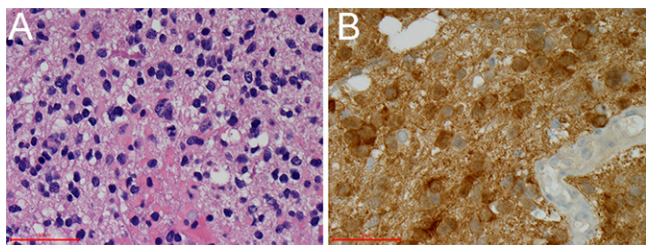


FIG. 3. Histopathology. **A:** Hematoxylin and eosin stain of lesional tissue. **B:** IHC staining of IDH1R132H. Original magnifications $\times 1000$.

adjuvant chemoradiotherapy with 54 Gy in 30 fractions and temozolomide was recommended.

Literature Review

To generate a list of individual patients with IDH-mutant brainstem gliomas, we searched PubMed for all articles containing the terms “brainstem/brain stem,” “glioma/gliomas,” and “IDH/IDH1/isocitrate” in the title or abstract. The search yielded 39 studies, all of which were

assessed for inclusion. Nine studies totaling 15 patients that included patient-level data for adult IDH-mutant brainstem gliomas were included in the review; 7 patients had survival data available (Table 1). Among the available patient-level data, we found a mean (standard deviation [SD]) age of 39.8 (12.9) years and a male-to-female ratio of 9:3. Histopathology revealed low-grade lesions (WHO grade II) in 9 of 15 cases (oligoastrocytoma in 3 cases, diffuse astrocytoma in 5 cases, astrocytoma not otherwise specified in 1 case) and high-grade lesions (WHO grades III/IV) in 6 of 15 cases (anaplastic astrocytoma in 3 cases, WHO grade III glioma not otherwise specified in 1 case, and glioblastoma in 2 cases). Of the 7 patients with survival data available, 3 had low-grade lesions, and 4 had high-grade lesions; median overall survival was 56 months (range 12–73.2 months).

Discussion

Observations

The effect of IDH mutation on both tumorigenesis and prognosis is unclear in brainstem gliomas. In the present review of the literature, we found a median overall survival of 56 months in 7 patients harboring IDH-mutant brainstem gliomas (WHO grades II–IV) with considerable histopathological and clinical heterogeneity. Although the overall

TABLE 1. Compendium of patients with IDH-mutant brainstem glioma

| Authors & Yr | Case No. | Age (yrs) | Sex | Histology | WHO Grade | Location | Contrast Enhanced? | Tx | IDH Mutation | Ki67/MIB-1 (%) | p53 | OS (mos) |
|--|----------|-----------|-----|-----------|-----------|----------|--------------------|-------------|--------------|----------------|-----|----------|
| Reyes-Botero et al., 2014 ¹⁹ | 1 | 31.2 | NR | OA | II | M | No | RT | R132C | 1 | Neg | 56 |
| Reyes-Botero et al., 2014 ¹⁹ | 2 | 40.8 | NR | GBM | IV | P | Yes | RT | R132G | 40 | Neg | 70.8 |
| Reyes-Botero et al., 2014 ¹⁹ | 3 | 49.4 | NR | OA | II | P/M | No | RT | R132H | 1 | Pos | 73.2 |
| Picca et al., 2018 ¹⁷ | 4 | 41 | F | AA | III | NR | No | RT/C | NR | 10 | NR | 44 |
| Picca et al., 2018 ¹⁷ | 5 | 66 | M | G | III | NR | No | RT | NR | 5 | NR | 29 |
| Theeler et al., 2015 ³ and Ellezam et al., 2012 ²⁴ | 6 | 40 | M | DA | II | M | Yes | C | R132H | NR | NR | >14* |
| Ellezam et al., 2012 ²⁴ | 7 | 24 | M | DA | II | M | NR | NR | R132H | NR | NR | NR |
| Theeler et al., 2015 ³ and Ellezam et al., 2012 ²⁴ | 8 | 56 | M | AA | III | P | No | RT | R132H | NR | NR | 12 |
| Javadi et al., 2018 ¹⁶ | 9 | 22 | F | A | II | P/M | No | Debulk/C/RT | R132H | 3 | NR | >24* |
| Waqar et al., 2014 ²⁵ | 10 | 34 | F | DA | II | P | Yes | RT/C | R132H | NR | NR | 61 |
| Uekawa et al., 2015 ²⁶ | 11 | 46 | M | DA | II | M | No | RT/C | R132H | 2–3 | Neg | >6* |
| Nejo et al., 2018 ²⁷ | 12† | 31 | M | DA | II | P | No | RT/C | R132C | <3 | Pos | >18* |
| Bonnet et al., 2016 ²⁸ | 13‡ | 30 | M | OA | II | NR | NR | NR | R132S | NR | NR | >36* |
| Theeler et al., 2015 ³ | 14 | 57 | M | GBM | IV | P | Yes | RT/C | R132H | NR | NR | >7* |
| Present study | 15 | 29 | M | AA | III | M | Faint | RT/C | R132H? | NR | Neg | N/A |

A = astrocytoma not otherwise specified; AA = anaplastic astrocytoma; C = chemotherapy; DA = diffuse astrocytoma; G = glioma not otherwise specified; GBM = glioblastoma multiforme; M = medulla oblongata; N/A = not applicable; Neg = negative; NR = not recorded; OA = oligoastrocytoma; OS = overall survival; P = pons; Pos = positive; RT = radiotherapy; Tx = treatment.

Case 15 is from our own case study. All IDH mutations are in IDH1, except in case 13 (IDH2 R132S mutation).

* Patient still alive at the time of data reporting.

† This patient was diagnosed with Maffucci syndrome and presented with IDH1 R132C–mutant pituitary adenoma and clival chondrosarcoma in addition to his brainstem tumor.

‡ This patient also had a diagnosis of Maffucci syndrome.

survival is slightly longer than previously reported in adult brainstem gliomas (30–40 months),⁴ it is similar to that in a recent study reporting an overall survival of 54.9 months for IDH1-mutant brainstem glioma.⁹ The aforementioned study did not demonstrate a statistically significant difference in overall survival between IDH1-mutant (54.9 months) and wild-type (38.4 months) brainstem gliomas. This is markedly different from supratentorial gliomas, in which the IDH mutation is associated with low-grade pathology, secondary glioblastoma multiforme, and improved prognostic value.¹² However, the size of the adult brainstem cohort in the literature is too small to permit safe conclusions and to allow solid comparisons between IDH-mutant and IDH wild-type counterparts.

The mechanism through which the IDH mutation drives tumorigenesis remains unclear. The favorable prognosis in supratentorial IDH-mutant gliomas is not reproduced in the setting of other cancers, including acute myelogenous leukemia, melanoma, and cholangiocarcinoma.¹⁵ Its role in diffuse brainstem glioma remains particularly elusive. Previous cohorts have reported the rate of IDH mutation in brainstem gliomas to be between 15% and 25%.^{9,16,17} Another study shows that 30% of brainstem and diencephalic gliomas harbor IDH mutations, significantly lower than supratentorial gliomas.¹⁸ IDH-mutant brainstem gliomas have also been associated with larger tumors, O⁶-methylguanine-DNA methyltransferase promoter methylation, TP53 mutations, and overall survival similar to that of IDH1/H3F3A co-wild-type brainstem gliomas.⁹ It is important to note that several IDH mutations have been identified and that the most common (R132H) is typically identified with IHC. Interestingly, one study found uncommon variants (R132G and R132C) to be more common than R132H in a small cohort of brainstem gliomas, suggesting that current practice may miss a significant proportion of these mutations.¹⁹ Nevertheless, even where IDH sequencing is available, cost and yield remain limitations.²⁰

Although IDH mutations in brainstem gliomas are rare, histone 3 mutations are much more common, occurring in up to 54% of cases.⁴ They are also associated with poor prognosis. Although there remains a need for larger cohorts, one study of 28 adult brainstem gliomas (19 WHO grade II, 9 WHO grade III/IV) found an overall median survival of 16.6 months (SD 12.2 months) with an H3 mutant hazard ratio of 4.42 (1.08–18.11 95% confidence interval).⁷ Another study of 25 patients with adult brainstem gliomas (7 with H3 mutation; 13 WHO grade I/II, 12 WHO grade III/IV) found a median overall survival of 9 months and >180 months in H3-mutant and wild-type tumors, respectively.⁶ The prognostic implications of H3 mutations in the context of WHO grade remain unclear.

The identification of major molecular subtypes in adult brainstem glioma may have important implications for therapeutics. It has become clear in the wake of several failed trials that a one-size-fits-all approach is not sufficient and that subgroup-specific targets will be needed to achieve success. For example, it has been shown that inhibition of H3K27 demethylase in mouse xenograft models of H3K27M-mutant pediatric DIPG is associated with reduced cell proliferation and viability.²¹ One case report documented complete radiological resolution using temozolomide, radiation, and the tyrosine kinase inhibitor apatinib in an adult with anaplastic IDH/H3 wild-type brainstem astrocytoma.²² The addition of chemotherapy with radiotherapy appears to be more fruitful in adult brainstem glioma than in pediatric cases, with the benefits of this combined approach appearing to be most significant in IDH-mutant tumors.⁴ Modest improvements in outcomes have also been achieved with the vascular endothelial growth factor inhibitor bevacizumab, though the effect is less than in supratentorial glioma.⁴

Clearly, there remains a need for the identification of novel, subgroup-specific molecular treatments for this disease.

Current scientific understanding allows us to postulate that brainstem gliomas are not a single biological entity and that brainstem lesions with IDH mutations may arise from or may be related to the cell of origin in supratentorial gliomas. However, there are no reports of concomitant brainstem and supratentorial gliomas, and the differential effect of the IDH mutation in these two diseases suggests fundamental differences in biology. Importantly, the epigenetic signatures in brainstem gliomas differ drastically between histone 3–mutated lesions and IDH-mutant lesions.^{21,23} It will be important to study adult brainstem gliomas in terms of these major molecular subtypes because they may represent unrelated entities with unique biological properties and effective therapies, but challenges remain, given the rarity of this disease. Advances in knowledge and therapies may thus rely in part on breakthroughs in more common and related diseases, such as pediatric brainstem gliomas and supratentorial gliomas.

Lessons

Adult IDH-mutant brainstem gliomas are rare and remain poorly understood. Our case is the 15th case reported to date. We suggest, in accordance with previous work, that IDH mutation does not have the same prognostic implications in the brainstem as it does for adult supratentorial gliomas. Given the degree of heterogeneity observed in these lesions, we advocate the need for larger molecular and clinical studies in the future in order to identify biologically homogeneous subgroups that may exhibit unique clinical features and/or treatment sensitivities.

References

1. Reyes-Botero G, Mokhtari K, Martin-Duverneuil N, et al. Adult brainstem gliomas. *Oncologist*. 2012;17(3):388–397.
2. Roux A, Pallud J, Saffroy R, et al. High-grade gliomas in adolescents and young adults highlight histomolecular differences from their adult and pediatric counterparts. *Neuro Oncol*. 2020;22(8):1190–1202.
3. Theeler BJ, Ellezam B, Melguizo-Gavilanes I, et al. Adult brainstem gliomas: correlation of clinical and molecular features. *J Neurol Sci*. 2015;353(1-2):92–97.
4. Hu J, Western S, Kesari S. Brainstem glioma in adults. *Front Oncol*. 2016;6:180.
5. Khuong-Quang DA, Buczkowicz P, Rakopoulos P, et al. K27M mutation in histone H3.3 defines clinically and biologically distinct subgroups of pediatric diffuse intrinsic pontine gliomas. *Acta Neuropathol*. 2012;124(3):439–447.
6. Daoud EV, Rajaram V, Cai C, et al. Adult brainstem gliomas with H3K27M mutation: radiology, pathology, and prognosis. *J Neuropathol Exp Neurol*. 2018;77(4):302–311.
7. Feng J, Hao S, Pan C, et al. The H3.3 K27M mutation results in a poorer prognosis in brainstem gliomas than thalamic gliomas in adults. *Hum Pathol*. 2015;46(11):1626–1632.
8. Wang L, Li Z, Zhang M, et al. H3 K27M-mutant diffuse midline gliomas in different anatomical locations. *Hum Pathol*. 2018;78:89–96.
9. Zhang Y, Pan C, Wang J, et al. Genetic and immune features of resectable malignant brainstem gliomas. *Oncotarget*. 2017;8(47):82571–82582.
10. Porkholm M, Raunio A, Vainionpää R, et al. Molecular alterations in pediatric brainstem gliomas. *Pediatr Blood Cancer*. 2018;65(1):e26751.
11. Huang J, Yu J, Tu L, et al. Isocitrate dehydrogenase mutations in glioma: from basic discovery to therapeutics development. *Front Oncol*. 2019;9:506.
12. Agnihotri S, Aldape KD, Zadeh G. Isocitrate dehydrogenase status and molecular subclasses of glioma and glioblastoma. *Neurosurg Focus*. 2014;37(6):E13.

13. Hartmann C, Hentschel B, Simon M, et al. Long-term survival in primary glioblastoma with versus without isocitrate dehydrogenase mutations. *Clin Cancer Res*. 2013;19(18):5146–5157.
14. Skjulsvik AJ, Bø HK, Jakola AS, et al. Is the anatomical distribution of low-grade gliomas linked to regions of gliogenesis? *J Neurooncol*. 2020;147(1):147–157.
15. Unruh D, Zewde M, Buss A, et al. Methylation and transcription patterns are distinct in IDH mutant gliomas compared to other IDH mutant cancers. *Sci Rep*. 2019;9(1):8946.
16. Javadi SA, Hartmann C, Walter GF, et al. IDH1 mutation in brain stem glioma: case report and review of literature. *Asian J Neurosurg*. 2018;13(2):414–417.
17. Picca A, Berzero G, Bielle F, et al. *FGFR1* actionable mutations, molecular specificities, and outcome of adult midline gliomas. *Neurology*. 2018;90(23):e2086–e2094.
18. Qi S, Yu L, Li H, et al. Isocitrate dehydrogenase mutation is associated with tumor location and magnetic resonance imaging characteristics in astrocytic neoplasms. *Oncol Lett*. 2014;7(6):1895–1902.
19. Reyes-Botero G, Giry M, Mokhtari K, et al. Molecular analysis of diffuse intrinsic brainstem gliomas in adults. *J Neurooncol*. 2014;116(2):405–411.
20. Nassiri F, Zadeh G, Aldape K. IDH mutation testing in gliomas—where do we draw the line? *Neuro Oncol*. 2017;19(12):1568–1569.
21. Ramaswamy V, Remke M, Taylor MD. An epigenetic therapy for diffuse intrinsic pontine gliomas. *Nat Med*. 2014;20(12):1378–1379.
22. Yu D, Han G, Liu H, et al. Treatment of adult brainstem glioma with combined antiangiogenic therapy: a case report and literature review. *OncoTargets Ther*. 2019;12:1333–1339.
23. Zhang L, Chen LH, Wan H, et al. Exome sequencing identifies somatic gain-of-function *PPM1D* mutations in brainstem gliomas. *Nat Genet*. 2014;46(7):726–730.
24. Ellezam B, Theeler BJ, Walbert T, et al. Low rate of R132H IDH1 mutation in infratentorial and spinal cord grade II and III diffuse gliomas. *Acta Neuropathol*. 2012;124(3):449–451.
25. Waqar M, Hanif S, Rath N, et al. Diagnostic challenges, management and outcomes of midline low-grade gliomas. *J Neurooncol*. 2014;120(2):389–398.
26. Uekawa K, Nakamura H, Shinjima N, et al. Adult diffuse astrocytoma in the medulla oblongata: molecular biological analyses including H3F3A mutation of histone H3.3. *NMC Case Rep J*. 2015;3(2):29–33.
27. Nejo T, Tanaka S, Ikemura M, et al. Maffucci syndrome complicated by three different central nervous system tumors sharing an IDH1 R132C mutation: case report. *J Neurosurg*. 2018;131(6):1829–1834.
28. Bonnet C, Thomas L, Psimaras D, et al. Characteristics of gliomas in patients with somatic IDH mosaicism. *Acta Neuropathol Commun*. 2016;4:31.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Landry, Ye, Purzner, Zadeh. Acquisition of data: Landry, Ye, Kalyvas, Gao. Analysis and interpretation of data: Landry, Ye, Kalyvas, Gao, Zadeh. Drafting the article: Landry, Ye. Critically revising the article: Ye, Purzner, Kalyvas, Mohan, O'Halloran. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Landry. Administrative/technical/material support: Purzner.

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