Journal of Neuropathology & Experimental Neurology, 2023, 1–5
https://doi.org/10.1093/jnen/nlad070
Letter to the Editor

OXFORD

Letter to the Editor

Brainstem oligodendroglioma, IDH-mutant, and 1P/19Q-codeleted: A potential diagnostic pitfall

Oumaima Aboubakr, MSc[1,2,3], Alice Métais, MD, MSc[1,3,4], Lauren Hasty[1], Raphaël Saffroy, MD[5], Marc Zanello, MD, PhD[2,3,4], Johan Pallud, MD, PhD[2,3,4], Frédéric Dhermain, MD, PhD[6], Pascale Varlet, MD, PhD[1,3,4], Arnault Tauziède-Espariat, MD, PhD[1,3,4]*

[1]Department of Neuropathology, GHU Paris-Psychiatry and Neurosciences, Sainte-Anne Hospital, Paris, France
[2]Department of Neurosurgery, GHU Paris-Psychiatry and Neurosciences, Sainte-Anne Hospital, Paris, France
[3]Université de Paris Cité, Paris, France
[4]Institute of Psychiatry and Neurosciences de Paris (IPNP), UMR S1266, INSERM, IMA-BRAIN, Paris, France
[5]Department of Biochemistry and Oncogenetics, Paul Brousse Hospital, Villejuif, France
[6]Radiation Oncology Department, Gustave Roussy University Hospital, Cancer Campus Grand Paris, Villejuif, France

*Send correspondence to: Arnault Tauziède-Espariat, MD, PhD, Department of Neuropathology. GHU Paris-Neurosciences, Sainte-Anne Hospital, 1, rue Cabanis, 75014 Paris, France; E-mail: a.tauziede-espariat@ghu-paris.fr

To the Editor:

The 2021 World Health Organization (WHO) Classification of Central Nervous System Tumors reinforces the concept of integrated diagnosis by defining essential histological and/or molecular criteria for each tumor type as well as relevant clinical information such as age and tumor location (1). According to the WHO 2021 CNS tumor classification, diffuse midline glioma, H3K27-altered belongs to the family of pediatric-type diffuse high-grade gliomas and is a good example since its definition combines clinical (mainly in a pediatric population), radiological (thalamus, basal ganglia, brainstem, spinal cord), histological (infiltrative glial proliferation), and molecular (histones gene mutations, EZHIP overexpression or *EGFR* alterations) information. Similarly, the integrated diagnosis of oligodendroglioma requires an IDH-mutation and a 1p/19q codeletion. The oligodendroglioma, IDH-mutant, and 1p/19q-codeleted tumor type has been mostly described in supratentorial locations with exceptional cases reported in the brainstem, posterior fossa, and spinal cord, with or without leptomeningeal spread. However, since most oligodendrogliomas were reported before the molecular era, differential diagnoses (particularly diffuse leptomeningeal glioneuronal tumor), cannot be confidently excluded (2–7). Herein, we report the case of an adult with a grade 2 brainstem oligodendroglioma, IDH-mutant 1p/19q-codeleted with complete clinical, radiological, pathological, and molecular characterization.

This case concerns a 59-year-old woman presenting with a 1-year history of binocular diplopia due to a left abducens nerve palsy and with a paralysis of the left facial nerve. The patient signed informed consent forms before surgery. Cerebral magnetic resonance imaging (MRI) showed a brainstem mass infiltrating the midbrain, pons, and medulla and extending to the left cerebellum with a hypointense signal on T1-weighted images, a hyperintense signal on T2-weighted, and FLAIR images and no contrast enhancement after gadolinium injection (Fig. 1A). The mass was diffuse, homogenously solid without a cyst component, perilesional edema, or apparent leptomeningeal attachment. There was no supratentorial lesion. Diffusion was not restricted. Neither hemorrhagic nor necrotic modifications were observed and no calcification was present on computed tomography. A MRI-based, robot-assisted, and image-guided stereotactic biopsy procedure (8) was achieved (8 biopsy samples) with no postoperative complication. Histopathological examination revealed a diffuse glial oligodendrodroglioma-like proliferation with high tumor cell density, low cytologic atypia, and entrapped neurons (Fig. 1B). No mitotic figures, necrosis, or microvascular proliferation were observed, and the MIB-1 labeling index was low (around 2%). The tumor cells intensely expressed Olig2. The expression of ATRX and of H3K27me3 was retained (Fig. 1B). There was no immunopositivity for IDH1R132H, H3K27M, EZHIP, or EGFR and no nuclear overexpression of p53 (Fig. 1B). A FISH analysis failed to reveal a chromosome 7 gain or *EGFR* locus (7p11.2) amplification and there was no *BRAF* rearrangement. DNA sequencing revealed an *IDH1* R132S mutation and a 1p/19q codeletion. Based on these features, the integrated diagnosis was a grade 2 oligodendroglioma, IDH-mutant and 1p/19q-codeleted (Fig. 1C). The DNA-methylation analysis copy number prediction confirmed

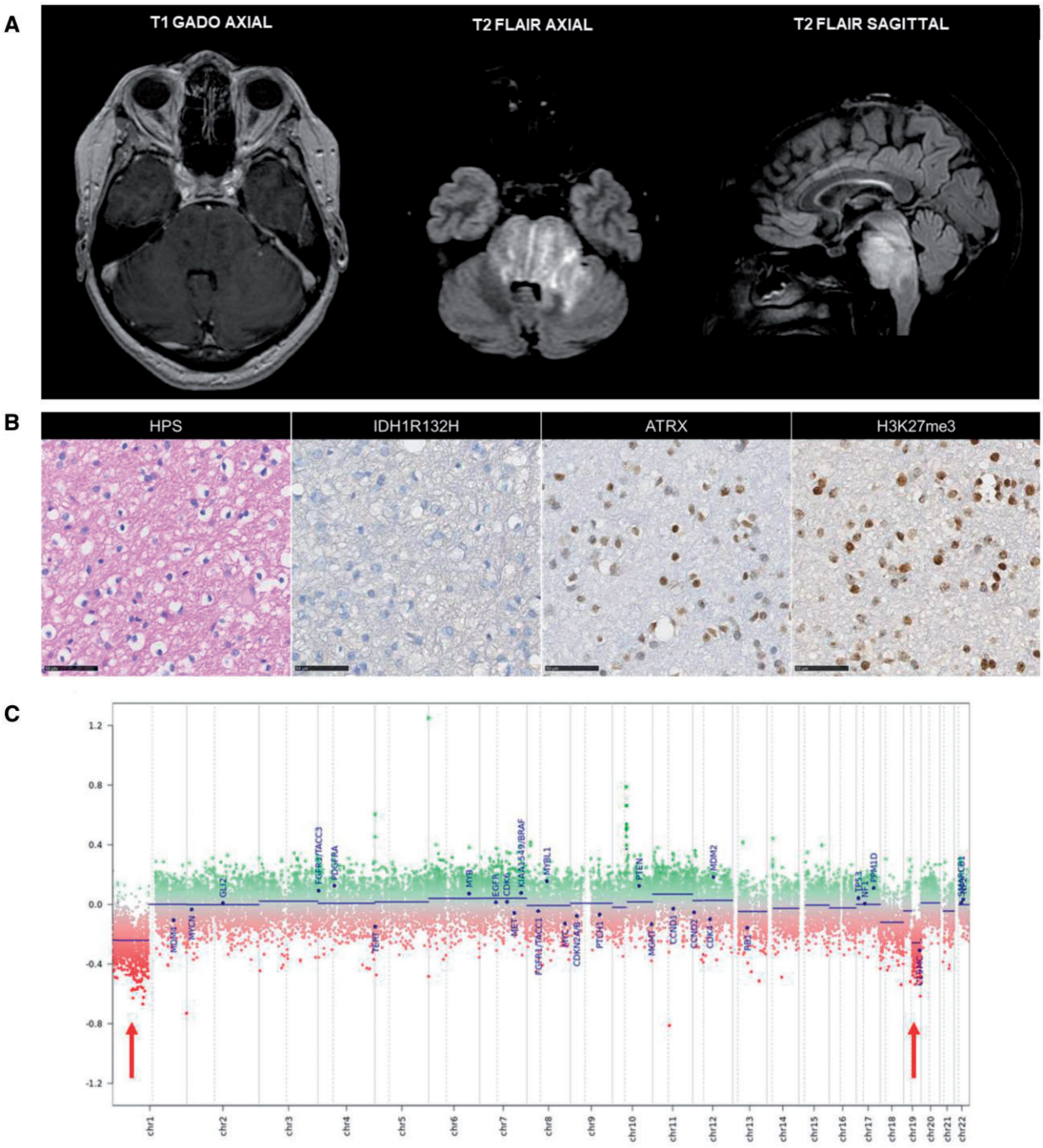

Figure 1. Radiological, histopathological, and molecular findings. **(A)** Magnetic resonance imaging (T1 with contrast and T2 FLAIR) of the lesion infiltrating the midbrain, pons, and medulla and extending to the left cerebellar hemisphere without contrast enhancement. **(B)** Common oligodendroglioma-like appearance (HPS, ×400), negative IDH1 R132H immunostaining (×400), retained expression of ATRX (×400), and H3K27me3 (×400). **(C)** Copy number prediction confirming 1p/19q codeletion. Scale bars: 50 µm.

the 1p/19q codeletion (Fig. 1C). The DKFZ/Heidelberg Brain/CNS Tumor Classifier classified the tumor as an oligodendroglioma, IDH-mutant and 1p/19q-codeleted with a calibrated score of 0.43 (v12.7). More commonly used v11b4 and v12.5 versions of the Classifier suggested the same diagnosis with lower calibrated scores of 0.21 and 0.20, respectively. One month after biopsy the patient was neurologically stable. Regarding the therapeutic strategy, the patient received chemotherapy (PCV; procarbazine, lomustine [CCNU]), followed by adjuvant radiation therapy (54 Gy total dose, 6-week duration).

To the best of our knowledge, this is the second reported case of an adult brainstem oligodendroglioma IDH-mutant, 1p/19q-codeleted diagnosed according to the current classification and the first with a DNA-methylation analysis. The

Table. Adult brainstem IDH-mutant glioma reported in the literature

Authors	Year	N° of cases	Histology	IDH mutation	1p/19q codeletion	H3 mutation	Age (years)
Nagase et al (10)	2023	1	Astrocytoma (n = 1)	IDH1R132H (n = 1)	NA	Negative	23
Iwahashi et al (11)	2023	4	Astrocytoma (n = 4)	IDH1 R132H (n = 1) IDH1 R132S (n = 2) IDH1 R132G (n = 1)	NA	Negative	24–38
Wang et al (12)	2022	16	Anaplastic astrocytoma (n = 2), Diffuse astrocytoma (n = 8), Glioblastoma (n = 2) NA (n = 4)	IDH1 R132H (n = 12) IDH1 R132C (n = 1) IDH2 (n = 3)	NA	Negative	NA
Zhou et al (13)	2022	5	Diffuse astrocytoma (n = 4), Low-grade glioma (n = 1)	IDH1 R132H (n = 4) IDH1 R132G (n = 1)	Negative or NA	H3K27 (n = 1)	29–52
Sano et al (14)	2021	1	Astrocytoma (n = 1)	IDH1 R132H (n = 1)	Negative	Negative	43
Ye et al (15)	2021	1	Anaplastic astrocytoma (n = 1)	IDH1 R132H (n = 1)	NA	Negative	29
Eschbacher et al (16)	2021	4	Anaplastic astrocytoma (n = 3), Glioblastoma (n = 1)	IDH1 R132C (n = 1) IDH1 R132S (n = 1) IDH1 R132H (n = 2)	NA	Negative	34–47
Chang et al (17)	2021	3	Diffuse astrocytoma (n = 1), Anaplastic astrocytoma (n = 1), Infiltrating glioma (n = 1)	IDH1 R132H (n = 2) IDH1 R132S (n = 1)	Negative	Negative	17–24
Banan et al (18)	2020	22	Astrocytoma (n = 22)	IDH1 R132H (n = 5) IDH1 R132C (n = 8) IDH1 R132G (n = 6) IDH1 R132S (n = 1) IDH2 R172S (n = 1) IDH2 R172G (n = 1)	Negative	H3K27 (n = 2)	1–68
Picca et al (19)	2018	6	Glioma, grade 2 (n = 1) Glioma, grade 3 (n = 4) Glioma, grade 4 (n = 1)	IDH1 R132H (n = 2) IDH1 R132G (n = 2) IDH1 R132C (n = 1) IDH1 R132L (n = 1)	Negative	Negative	20–75
Javadi et al (20)	2018	1	Astrocytoma (n = 1)	IDH1 R132H (n = 1)	NA	NA	22
Zhang et al (21)	2017	9	NA (n = 9)	IDH1 R132 (n = 9)	NA	Negative	20–54
Uekawa et al (22)	2016	1	Diffuse astrocytoma (n = 1)	IDH1 R132H (n = 1)	NA	Negative	46
Bonnet et al (23)	2016	1	Oligoastrocytoma (n = 1)	IDH2 R132S (n = 1)	Negative	NA	30
Hodges et al (9)	2015	1	Oligodendroglioma (n = 1)	IDH2 R172M (n = 1)	Yes	NA	42
Reyes-Botero et al (24)	2014	3	Oligoastrocytoma (n = 2), Secondary glioblastoma with oligodendroglial component (n = 1)	IDH1 R132H (n = 1) IDH1 R132G (n = 1) IDH1 R132C (n = 1)	Negative or NA	Negative or NA	31–49
Waqar et al (25)	2014	1	Astrocytoma (n = 1)	IDH1 R132H (n = 1)	NA	NA	34
Ellezam et al (26)	2012	3	Diffuse astrocytoma (n = 2), Anaplastic astrocytoma (n = 1)	IDH1 R132H (n = 3)	NA	NA	24–53

calibrated v12.7 score <0.9 could be explained by a low amount of total DNA or by the fact that all the other oligodendrogliomas in the classifier are supratentorial. The other reported case of a brainstem oligodendroglioma with IDH mutation and 1p/19q codeletion (9) was a 42-year-old man with a grade 3 oligodendroglioma, *IDH2*-mutant, 1p/19q-codeleted located in the pons. Following a biopsy, he received radiation, concomitant temozolomide for 6 weeks and 12 adjuvant cycles of temozolomide. Following treatment, brain MRIs showed a radiographic response, and he was clinically stable. Because cases reported in the past were often poorly molecularly characterized, the prevalence of oligodendroglioma, IDH-mutant, and 1p19q-codeleted in the brainstem may be underestimated. Further reports on brainstem oligodendrogliomas, IDH-mutant and 1p19q-codeleted are needed to determine if their prognosis differs from those with a supratentorial location and to define the best therapeutic implications. While they are rare in this location, we have found 83 documented cases of adult brainstem glioma, IDH-mutant in the literature in addition to the present case (9–26) (Table); most are IDH-mutant astrocytomas. Interestingly, non-IDH1-R132H variants are more frequent than in supratentorial IDH-mutant glioma (51% *IDH1*R132H, 39% *IDH1* non-R132H variants, 10% *IDH2* in our review) (18, 24, 26). While our case was negative for histone gene mutations, there have been 3 published cases of concomitant IDH and *H3* mutations (13, 18). Concerning prognosis, IDH-mutant gliomas may have a better outcome compared to other brainstem tumors, similar to cases with a supratentorial location. In 2022, Wang et al reported a retrospective series of 96 adult diffuse intrinsic pontine gliomas, 16 of them were IDH-mutant and 19 were H3K27-mutant; they reported a median overall survival of 43.8 months for IDH-mutant cases compared to 11.4 months for H3K27-mutant cases (12). Oligodendroglioma, IDH-mutant may be a potential diagnostic pitfall in case of diffuse infratentorial glioma in adult patients because diffuse intrinsic brainstem gliomas only account for 1–2% of adult gliomas (27). Routine histological diagnosis cannot rely on the IDH1R132H hallmark immunostaining since non-IDH1-R132H variants were more frequently described in infratentorial than in supratentorial IDH-mutant gliomas (18, 24, 26). This diagnosis may be particularly challenging considering the differential diagnoses encountered in this location (pilocytic astrocytoma, high-grade astrocytoma with piloid features, rare forms of purely intraparenchymal diffuse leptomeningeal glioneuronal tumor and diffuse midline glioma H3K27-altered). For all of these reasons, we recommend combining histopathological analysis with systematic genetic testing for *IDH1/2* and histone gene mutations for gliomas in this location in adult patients for an accurate integrated diagnosis.

FUNDING

No funding is reported.

ACKNOWLEDGEMENTS

We would like to thank technicians of the Department of Neuropathology for their assistance.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

This study was approved by the GHU Paris Psychiatrie Neurosciences, Sainte Anne Hospital's local ethic committee.

REFERENCES

1. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: A summary. Neuro Oncol 2021;23:1231–1251
2. Baran O, Kasimcan O, Oruckaptan H. Cerebellar peduncle localized oligodendroglioma: Case report and review of the literature. World Neurosurg 2018;113:62–66
3. Hewer E, Beck J, Vassella E, Vajtai I. Anaplastic oligodendroglioma arising from the brain stem and featuring 1p/19q co-deletion. Neuropathology 2014;34:32–8
4. Packer RJ, Sutton LN, Rorke LB, et al.Oligodendroglioma of the posterior fossa in childhood. Cancer 1985;56:195–199
5. Fukuoka K, Yanagisawa T, Watanabe Y, et al. Brainstem oligodendroglial tumors in children: Two case reports and review of literatures. Childs Nerv Syst 2015;31:449–55
6. Furtado SV, Venkatesh PK, Ghosal N, et al. Clinical and radiological features of pediatric cerebellar anaplastic oligodendrogliomas. Indian J Pediatr 2011;78:880–3
7. Wang KC, Chi JG, Cho BK. Oligodendroglioma in childhood. J Korean Med Sci 1993;8:110–6
8. Deboeuf L, Moiraghi A, Debacker C, et al. Feasibility and accuracy of robot-assisted, stereotactic biopsy using 3-dimensional intraoperative imaging and frameless registration tool. Neurosurgery 2023;92:803–811
9. Hodges SD, Malafronte P, Gilhooly J, et al. Rare brainstem oligodendroglioma in an adult patient: Presentation, molecular characteristics and treatment response. J Neurol Sci 2015;355:209–10
10. Nagase T, Ishida J, Sasada S, et al. IDH-mutant astrocytoma arising in the brainstem with symptom improvement by foramen magnum decompression: A case report. NMC Case Rep J 2023;10:75–80
11. Iwahashi H, Nagashima H, Tanaka K, et al. 2-Hydroxyglutarate magnetic resonance spectroscopy in adult brainstem glioma. J Neurosurg 2023;139:355–362
12. Wang Y, Pan C, Xie M, et al. Adult diffuse intrinsic pontine glioma: Clinical, radiological, pathological, molecular features, and treatments of 96 patients. J Neurosurg 2022;137:1628–1638
13. Zhou J, Lai M, Ni Y, et al. Case report: Clinicopathological and genetic features of IDH-mutant brainstem glioma in adults: Report of five cases. Pathol Oncol Res 2022;28:1610408
14. Sano K, Matsuda KI, Kawanami K, et al. Malignant progression of an IDH mutant brainstem glioma in adult. NMC Case Rep J 2021;8:301–307
15. Ye VC, Landry AP, Purzner T, et al. Adult isocitrate dehydrogenase-mutant brainstem glioma: Illustrative case. J Neurosurg Case Lessons 2021;1:CASE2078
16. Eschbacher KL, Ida CM, Johnson DR, et al. Diffuse gliomas of the brainstem and cerebellum in adults show molecular heterogeneity. Am J Surg Pathol 2021;45:1082–1090

17. Chang EK, Smith-Cohn MA, Tamrazi B, et al. IDH-mutant brainstem gliomas in adolescent and young adult patients: Report of three cases and review of the literature. Brain Pathol 2021;31: e12959
18. Banan R, Stichel D, Bleck A, et al. Infratentorial IDH-mutant astrocytoma is a distinct subtype. Acta Neuropathol 2020;140:569–581
19. Picca A, Berzero G, Bielle F, et al. FGFR1 actionable mutations, molecular specificities, and outcome of adult midline gliomas. Neurology 2018;90:e2086–e2094
20. Javadi SA, Hartmann C, Walter GF, et al. IDH1 mutation in brain stem glioma: Case report and review of literature. Asian J Neurosurg 2018;13:414–417
21. Zhang Y, Pan C, Wang J, et al. Genetic and immune features of resectable malignant brainstem gliomas. Oncotarget 2017;8: 82571–82582
22. Uekawa K, Nakamura H, Shinojima N, et al. Adult diffuse astrocytoma in the medulla oblongata: Molecular biological analyses including H3F3A mutation of histone H3.3. NMC Case Rep J 2016;3:29–33
23. Bonnet C, Thomas L, Psimaras D, et al. Characteristics of gliomas in patients with somatic IDH mosaicism. Acta Neuropathol Commun 2016;4:31
24. Reyes-Botero G, Giry M, Mokhtari K, et al. Molecular analysis of diffuse intrinsic brainstem gliomas in adults. J Neurooncol 2014; 116:405–11
25. Waqar M, Hanif S, Rathi N, et al. Diagnostic challenges, management and outcomes of midline low-grade gliomas. J Neurooncol 2014;120:389–98
26. 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;124:449–51
27. Ostrom QT, Price M, Neff C, et al. CBTRUS statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2015-2019. Neuro Oncol 2022;24:v1–v95