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Case Report

Case Report: Evolutionary Clinical-Radiological Features of a Diffuse Hemispheric Glioma, H3 G34 Mutant with Over 5 Years of Survival

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Abstract
Diffuse hemispheric glioma (DHG), H3 G34 mutant was included in the 5th edition of the World Health Organization Classification of Tumors of the Central Nervous System recently published. Given the recent inclusion in the current classification and its rarity in adult patients, there are scarce data on clinical-radiological characteristics, survival, and outcome. The authors report the case of a 35-year-old female with DHG, H3 G34-mutant characteristics and outcomes with an unusual presentation, recurrence, and prolonged survival. In conclusion, our case report demonstrates relevant details that should be observed in patients with suspicion or confirmation of the diagnosis of DHG, H3 G34 mutant, not only in the initial presentation but also in the evolution to ensure more personalized treatment.

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Introduction

Diffuse hemispheric glioma (DHG), H3 G34 mutant was included in the 5th edition of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (CNS5) recently published (2021) [1]. Despite being classified as a pediatric-type diffuse high-grade glioma (median age: 15–19 years), it can rarely affect adults [1, 2]. In contrast to the diffuse midline glioma, H3 K27-altered locates near the midline, DHG, H3 H34 mutant is usually located in the cerebral hemispheres. This tumor presents somatic missense mutation of the H3-3A gene, resulting in one of the following substitutions of histone H3: c.103G>A p.G35R (G34R), c.103G>C p.G35R (G34R), or c.104G>T p.G35V (G34V) [1]. These mutations result in translational modifications, altering the methylation status of lysine at position 36 [3]. The integrity of histones is essential because they stabilize chromatin and compact DNA and regulate access to regulatory factors [4]. Given the recent inclusion in the current classification and its rarity in adult patients [5, 6], there are scarce data on clinical-radiological characteristics, survival, and outcome. Therefore, we report the characteristics and outcomes of a case with an unusual presentation, recurrence, and prolonged survival.

Case Report

The 35-year-old female presented in July 2016 with visual alteration followed by a severe headache, unresponsive to analgesics. Magnetic resonance imaging (MRI) (Fig. 1) showed an expansive solid-cystic mass lesion centered in the right occipital lobe, with a predominant lateral cystic component and an enhancing medial solid component adjacent to the torcula, which showed mild restricted diffusion. There was no low susceptibility signal to suggest a hemorrhagic or calcified component. In addition, the arterial spin labeling technique demonstrated no increased perfusion. She underwent gross total resection on August 25, 2016, and histologically showed a highly cellular tumor, resembling CNS embryonal tumors' morphology, with high mitotic activity, microvascular proliferation, and necrosis. Immunohistochemical showed positivity in S100 and p53; loss of ATRX expression; and negativity for GFAP, OLIG2, EGFR, IDH1, and cytokeratin. The Ki67 was 80% (Fig. 2). Sequencing showed the following findings: ATRX G573fs*10, H3F3A G35R, and TP53 Q317*; 1.26 mutation-per-megabase; and stable microsatellite. These findings corroborated the diagnosis of the DHG, H3G34 mutant.

Complementary treatment with stereotactic radiotherapy with 60 Gy in 30 fractions of 2 Gy and concomitant and sequential temozolomide with doses of 75 mg/m^2 daily during radiotherapy and 150 mg/m^2 in cycle 1/200 mg/m^2 D1 to D5 every 28 days for 18 cycles until May 2018. In February 2020, she presented with left hemiparesis, and the MRI demonstrated a new area of restricted diffusion and increased fluid-attenuated inversion recovery signal in the white matter of the right corona radiata and centrum semiovale, with no contrast enhancement (Fig. 3). In addition, the cerebral blood volume as per the dynamic susceptibility contrast perfusion technique depicted increased cerebral blood volume. Then, she started treatment with temozolomide rechallenge for three cycles without response. We changed the systemic therapy for lomustine plus bevacizumab, performed from May 2020 to January 2021 when we evidenced a new progression in a nonirradiated area with lesions in the body of the corpus callosum and left corona radiata, with marked diffusion restriction (Fig. 3). The patient was then treated with intensity-modulated radiation therapy at a dose of 35 Gy (10 fractions of 3.5 Gy) and maintained systemic treatment until October 2021. We opted for chemo-vacation

Fig. 1. Solid-cystic lesion with epicenter in the right occipital lobe (**a**, **b**) and heterogeneously enhancing solid component adjacent to the torcula (**c**, **d**), showing mild restricted diffusion (**e**, **f**), delineating a central area of necrosis. No associated hemorrhagic or calcified component (**g**) or increased perfusion (**h**). Sequences: axial FLAIR (**a**), sagittal T1 (**b**), axial and coronal T1 post-contrast (**c**, **d**), axial DWI and ADC map (**e**, **f**), axial SWI (**g**), and axial ASL (**h**). ASL, arterial spin labeling; FLAIR, fluid-attenuated inversion recovery.

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Fig. 2. a Pathological and immunohistochemical analysis: highly cellular tumor, resembling CNS embryonal tumors' morphology; hematoxylin and eosin (HE), magnification ×40. **b** Spontaneous micronecrosis, HE magnification ×100. **c** Atypia, mitosis, and microvascular proliferation; HE, magnification ×200. **d** P53 mutated, magnification ×100. **e** GFAP negative, magnification ×100. **f** Loss of ATRX expression, magnification ×100. **g** OLIG2 negative, magnification ×100. **h** EGFR negative, magnification ×100. **i** IDH-1 negative, magnification ×100. **j** Ki67 80%, magnification, ×200.

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Fig. 3. a Immediate postoperative imaging shows no residual tumor. 2020: a new area of increased FLAIR signal (**b**) and restricted diffusion (**c**) in the white matter of the right corona radiata and centrum semiovale, with increased perfusion (**d**) as per DSC technique. 2021: new markedly restricted lesions in the body of the corpus callosum (**e**) and left corona radiata (**f**). 2022: new progression to both cerebral hemispheres (**g**) with heterogeneous contrast enhancement (**h**). FLAIR, fluid-attenuated inversion recovery; DSC, dynamic susceptibility contrast.

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due to stable disease and fatigue as limiting toxicity. In February 2022, the patient presented a worsening neurological condition, with more frequent headaches and worsening left hemiparesis and the onset of right paresthesia. MRI showed a new lesion extending to both cerebral hemispheres and heterogeneous enhancement, inferring disruption of the brain-blood barrier (Fig. 3). Reintroduction of bevacizumab was performed with no significant improvement clinically or radiologically. The best supportive care exclusive was offered, and the patient died on March 18, 2022. The survival from the diagnosis until death was 5 years and 7 months. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000530181).

Discussion

The DHG, H3 G34 mutant is a new type of glioma that has recently been included in CNS5, and therefore, its knowledge is still being built, especially in the adult population, which is rarely affected. The diagnostic criteria established by this classification are essential: infiltrative glioma with high mitotic activity and hemispheric location and mutation H3.3p.G35R (G34R) or p.G35V (G34V); desirable: OLIG 2 immunonegativity, loss of ATRX expression, and diffuse p53 immunopositivity [1]. Among the most described imaging findings are single or multifocal lesions, cortico-subcortical with hemispheric localization, in or a faint contrast enhancement, little delimited limits, infiltrative lesions mainly frontoparietal or temporo-insular, and areas of ADC restriction on diffusion-weighted imaging [2, 7, 8]. A recent systematic review that analyzed 20 studies with reports of 257 cases with the DHG, H3 G34 mutant reported a median age at diagnosis of 17 years (range 14–23), no gender predilection, the predominance of the H3.3 G34R mutation, and a median overall survival of 14.4 months (10.1–26 months) [3].

In this report, we present, in detail, the clinical, anatomopathological, and mainly radiological features of a patient with DHG, H3 G34 mutant. Differently from the one previously described, our patient was diagnosed with a higher age than described in the literature (35 vs. 17 years) and presented a more indolent evolution than expected for high-grade gliomas in general and with the available data of the DHG, H3 G34 mutant, totaling a survival of 5 years and 7 months. Regarding histological characteristics, we observed similar findings to those described in previous reports [2] and the CNS5 [1]. It is important to emphasize that the mutation histone test should be performed in young adult patients with high-grade DHGs IDH wildtype, guided by morphological findings, obviously in places where this research is not routinely performed, such as in Brazil. When the test is unavailable, the term NOS (not otherwise specified) must be added to the diagnostic, according to CNS5 [1]. The most important findings in this case are the distinct MRI features. These patients may present with lesions suggestive of high-grade diffuse gliomas, such as enhancement and necrosis, but may also have lower grade findings. Still, the most striking in our case was diffusion restriction in ADC, which is consistent with a high cellularity of this tumor. We observed this characteristic in the initial lesion with improvement during the phases in which the patient responded to treatment and new areas of restricted diffusion in recurrences. This finding anticipated the appearance of symptoms and the new regions of enhancement in MRI. In this type of diffuse glioma, by our observations, diffusion restriction seems to be a marker not only diagnostic but also a prognosis and predictive response to the therapy employed, but this finding should still be validated in prospective future studies.

Conclusion

We report a new DHG, H3 G34-mutant case with its clinical characteristics and pathological as well distinct MRI findings. Despite the poor prognosis (median 12–24 months), our case survived for more than 5 years. We demonstrate relevant details that should be observed in patients with suspicion or confirmation of the diagnosis of the DHG, H3 G34 mutant, not only in the initial presentation but also in the evolution to ensure more personalized treatment.

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Statement of Ethics

Written informed consent for the publication of this case report and any accompanying images was obtained from the next of kin of the patient. Ethical approval is not required for this study in accordance with local or national guidelines.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Data acquisition: C.A.F.Y. and M.S; drafting of the manuscript: C.A.F.Y, M.S., and C.L.P.L; critical revision of the manuscript: L.L.F.A., C.M.S.C., P.L.M., and F.E.A.C.N; final approval to be published: C.A.F.Y. and C.L.P.L.

Data Availability Statement

All data are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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