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Diffuse Midline Glioma H3 K27-Mutant in an Adult: A Rare Case

Case Report

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Abstract

Diffuse midline glioma, H3K27M-mutant, WHO grade IV (DMGM), is a newly established entity in the 2016 WHO classification. It is uncommon and the median age of diagnosis is 5-11 years. Due to their rarity in adults, their recognition can be challenging even though the histopathology and phenotypes of adult and pediatric cases are similar. We report a case of a middle-aged female who presented with seizures and persistent headache, where imaging revealed an enhancing suprasellar mass involving the hypothalamus and fornix and she was diagnosed with H3K27M-mutant diffuse midline glioma. DMGM is extremely rare in adults and therefore, more cases need to be reported to enable their recognize among neuropathologists. Also, this report suggests a needed emphasis on obtaining molecular studies whenever possible if there is a suspicion of H3K27M-mutant DMGM, given that they are extremely aggressive and have poor clinical outcomes in most cases. The case was presented at College of American Pathologists (CAP) annual conference in Chicago (October 2018) and the abstract was published in Archives as an online supplement only.

Keywords: Glioma; Suprasellar; Hypothalamus; Fornix; Midbrain; Thalamus

Introduction

Diffuse midline glioma, H3K27M-mutant, WHO grade IV (DMGM), is an aggressive malignancy which tends to have widespread invasion and involvement of adjacent structures [1]. They are rare tumors with most cases reported in the age range of 5-11 years. Due to the availability of widespread molecular studies, the literature is making more reports available, which can help us understand the different patterns and morphology of this entity, along with its defining the criteria. Most of these gliomas have some areas of classic astrocytic morphology, with ovoid nuclei containing coarse chromatin and histone H3-K27M mutant protein staining is usually diffusely positive in the neoplastic tumor cell nuclei, with no nuclear staining seen in endothelial cells, inflammatory cells, or entrapped non-neoplastic neurons and glial cells [2]. Adult DMGM is rare with only a few cases reported in literature [3,5,7,8]. We present a rare case of an adult patient with diffuse midline glioma harboring H3K27M mutation in the hypothalamus, in order to increase the awareness if this entity among our pathologist colleagues.

Case Presentation

Our patient was a middle aged female with no prior comorbidity who was referred to our medical center with an acute onset of seizure and persistent headache. After the MRI showed an enhancing suprasellar mass involving the hypothalamus and fornix, the patient underwent tumor resection surgery and the resected tissue was submitted for histopathological examination (Figure 1).

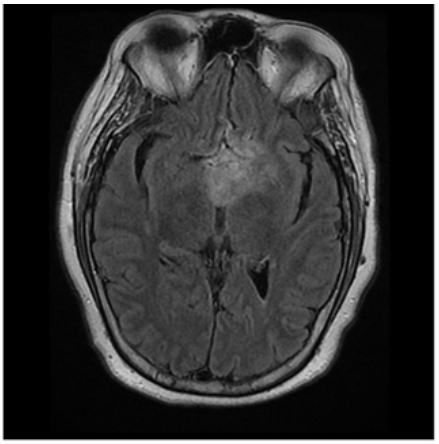

Figure 1: T1 weighted images show a distorted thalamus that is strongly enhanced on gadolinium.

Hematoxylin and Eosin-stained sections of the resected mass showed a neoplastic glial proliferation (A, B and C: 20x, 60x and 10x respectively) with endothelial proliferations. In addition, the tumor cells were largely negative (D) for Glial Fibrillary Acidic Protein (GFAP) and only focally positive for synaptophysin (G), and they were positive for H3K27M (F) and negative for H3K27Me3 (E). The labeling index for Ki67 (H) was homogeneously high (about 50%). Some necrosis was present but there was no pseudopalisading necrosis. The final diagnosis was H3K27M-mutant diffuse midline glioma. The patient outcome is unknown as a patient was lost to follow up which is a major limitation of this case report (Figure 2).

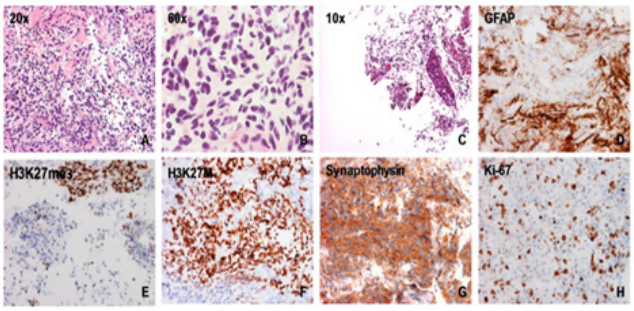

Figure 2: Hematoxylin and eosin-stained sections of the resected mass showed a neoplastic glial proliferation (A, B and C: 20x, 60x and 10x respectively) with endothelial proliferations. In addition, the tumor cells were largely negative (D) for Glial Fibrillary Acidic Protein (GFAP) and only focally positive for synaptophysin (G) and were positive for H3K27M (F) and negative for H3K27Me3 (E). The labeling index for Ki67 (H) was homogeneously high (about 50%).

Discussion

Diffuse midline glioma, H3K27M-mutant, WHO grade IV (DMGM) was introduced as a newly established entity in the 2016 WHO classification. They occur mostly in pediatric patients and their significance in adult patients is underestimated. For the diagnosis of diffuse midline glioma, H3 K27M-mutant, a tumor should have the following criteria: be diffuse, be in the midline, be a glioma and have a H3 K27M mutation in the H3F3A or HIST1H3B/C genes. If a tumor does not meet all four of these features, even if it has an H3 K27M mutation it should not be diagnosed as a diffuse midline glioma, H3 K27M-mutant [4].

Histologically, DMGMs show infiltrating glioblastoma features with a microvascular proliferation. The nuclei are positive for the histone H3 K27M mutant protein and, GALP and OLIG2, but negative for IDH1R132H. High Ki67 labeling is common [5]. Glioblastoma, neurocytoma, glioneuronal tumors and embryonal tumor of the CNS are some entities included in the differential diagnosis of DMGM with, particularly when those tumors have high cellularity [5]. Their midline location suggests that H3 K27M mutations are oncogenic in progenitors implicated in the midline structures development. The specific location on the midline varies with age among adults, and H3 K27M-mutant gliomas are frequently located in the thalamus and in the spine, whereas in children they are usually located within the pons [6]. Adult DMGM is infrequent and it is even rarer for the tumor to be found in the hypothalamus.

In comparing adult DMGM with other high-grade gliomas, fewer CDKN2A/B, TERTp and PTEN mutations are observed. IDH1/IDH2 and EGFR alterations are absent in H3 K27M mutated patients, but also both alterations are missing in the H3 K27M wild type adult DMG patients [7]. For this reason, the diagnosis of DMG H3 K27M requires the tumor to be diffuse, besides being midline, glioma and H3K27M mutant. With all four criteria, contrary to the pediatric literature, no differences in survival are identified when we compare this tumor to non-midline high-grade glioma [8]. All reported adult cases of DMG H3 K27M have an aggressive behavior. However, it is noted the prognosis of H3 K27M-mutant gliomas is better when the tumor is in unusual anatomical locations compared with tumors located in the brainstem [9].

DMGM H3 K27M mutations are inoperable and without a cure, mostly because of the nature of the tumor and its anatomic location. Surgery is often used for diagnostic purposes. Promising techniques such as Convection-Enhanced Delivery (CED) bypass of the blood-brain barrier, with hydraulic pressure, enhance effective delivery of a therapeutic agent into a target region [10]. Therefore, CED represents a possible method of treating midline tumors with the H3K27M mutation. The importance of a better characterization of the molecular alterations of these tumors with larger multi-institutional studies is evident, for prognosis and treatment.

Conclusion

The diagnosis of DMGM is largely characterized by its combination of morphologic, immunophenotypic and molecular features and the rarity of this tumor may lead to diagnostic challenges. Due to their rarity, the diagnostic criteria of DMGB are more challenging in adults and pathologists should be aware of them, particularly because they may be easily misdiagnosed as other tumors sharing similar criteria. In our adult DMGM, the presence of endothelial proliferation, variable negative expression of GFPA, variable positive expression of synaptophysin and a 50% mutation rate of P53, could have easily suggested other incorrect diagnoses, such as glioblastoma, neurocytoma, glioneuronal and embryonal CNS tumors. Hypothalamic DMGM is extremely rare in adults and makes this diagnosis even more challenging. However, the presence of endothelial proliferation and a very high Ki67 labeling index helps in diagnosing DMGM. DMGM should be considered as the differential diagnosis in any midline brain lesion and molecular genetic testing should be ordered to confirm the diagnosis.

Submission Declaration and Verification

Parts of this case were presented at College of American Pathologists (CAP) annual conference in Chicago (October 2018) and the abstract was published in Archives as an online supplement only.

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable (no identifying information is present in the case report).

Availability of Data and Materials

Not applicable.

Competing Interests

None

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None

Authors' Contributions

All authors contributed equally in preparing the manuscript

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