Case Report

The H3.3K27M Mutation and its Role in Pediatric Midline Gliomas: Case Report and Review of the Literature

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Abstract

First identified in 2012, the histone 3 mutation H3.3K27M significantly affects the prognosis of children with anaplastic astrocytoma (AA) and other gliomas. Tumors with this mutation tend to be more aggressive and localize along the midline, behaving like diffuse intrinsic pontine gliomas (DIPGs). Surgical options are often limited because of the deep location of these tumors coupled with their invasive and infiltrative nature. Additionally, AA with this histone mutation is more resistant to chemotherapy and radiation treatment. Given this aggressive and resistant behavior, children with thalamic and/or hypothalamic AA with this mutation have a lower than expected life expectancy of roughly 1 year. In this case report of an 11-year-old female with anaplastic astrocytoma and the H3.3K27M variant, the authors describe the diagnostic importance of genetic and/or immunohistochemistry testing to identify this mutation. We review the relevant literature about the H3.3K27M mutation and discuss the implications that the mutation may have on the management of children with these neoplasms.

INTRODUCTION

Anaplastic astrocytoma (AA), a World Health Organization (WHO) grade III astrocytoma, is a rare (0.44 per 100,000 persons) [1,2] and malignant (5-year relative survival rate of 23.6%) [3] tumor of the central nervous system (CNS). AA can occur anywhere within the CNS including the cerebellum, cerebral cortex, central areas of the brain, brainstem and spinal cord [1]. AA occurs primarily in adults with a median age of diagnosis between 43 and 53 [1,2,4,5], and is nearly twice as likely to develop in males [1,2,4,6] and Caucasians [2,4] compared to females and African Americans, respectively.

H3.3K27M is a Lys 27-to-methionine mutation at one allele of H3F3A, one of two genes encoding the histone 3 (H3) variant H3.3 [7]. Recent studies have implicated the H3.3K27M mutation in up to sixty percent of pediatric high-grade gliomas [7]. In over ninety percent of pediatric thalamic high-grade astrocytomas, the H3.3K27M has also been identified [8]. The H3.3K27M mutation in a child with an anaplastic astrocytoma is associated with a median survival of approximately one year following diagnosis [7]. Gliomas with this mutation tend not only to be particularly aggressive but also to be localized along the midline, often making surgical resection significantly more challenging [8].

A case of an 11-y.o. African-American female with a midline thalamic AA and the H3.3K27M mutation is presented. Based on the aggressive behavior of high-grade astrocytoma and the presence of the H3.3K27M mutation, we suggest that genetic profiling of midline gliomas be conducted in order to more quickly and effectively diagnose patients with these tumors.

CASE PRESENTATION

History and examination

An 11-year-old right-handed African American female with no significant medical history presented with generalized headaches and nausea with emesis. Her headaches had started...
approximately six months prior to presentation. On presentation, all vital signs were normal and her physical and neurological examinations were normal except for severe bilateral papilledema. A computed tomography (CT) scan of the head showed obstructive hydrocephalus with a mass in the posterior aspect of the third ventricle (Figure 1). The mass was hypodense on CT with punctate calcifications.

Magnetic resonance imaging (MRI) of the brain was done with and without intravenous (IV) contrast showing a midline neoplasm originating from the thalamic-hypothalamic area that was slightly hypointense on T1 imaging with minimal enhancement (Figure 2). The mass, approximately 1.8 cm x 1.4 cm x 1.6 cm, was located anterior to the pineal region, above the dorsal midbrain. Some punctate calcifications were noted in the thalamus on the left. Differential diagnosis included: hamartoma, thalamic glioma, pineal astrocytoma, pineoblastoma, germinoma, teratoma, dysgerminoma, and meningioma.

**Operation and postoperative course**

An endoscopic third ventriculostomy (ETV) was performed. An endoscopic biopsy of the tumor, which presented just below the thalamic adhesion in the third ventricle, was conducted through the same anterior burr hole. An external ventricular drain was left in place. A ventriculoperitoneal shunt was eventually required for definitive management of obstructive hydrocephalus, despite a functional ETV. Frozen section of the biopsy was suggestive of glioma. On hematoxylin and eosin (H&E) staining, markedly atypical and pleomorphic astrocytes are seen, and occasional mitotic figures identified, diagnostic of a malignant astrocytic neoplasm (Figure 3). Ki67 labeling was 5-8% in the most proliferative areas.

Molecular testing demonstrated the presence of the H3.3K27M mutation and confirmed the diagnosis of AA. By iFISH (FC-16-423), there was no amplification of platelet derived growth factor receptor alpha (PDGFRα), endothelial growth factor receptor (EGFR), or hepatocyte growth factor receptor (MET). There was no duplication or rearrangement of serine/threonine-protein kinase B-Raf (BRAF), and no deletion of phosphatase and tensin homolog (PTEN) was detected.

Surgical resection of the tumor was discussed with the family, but since a gross total excision was not feasible due to the tumor’s location, the family opted for chemotherapy, radiation and non-surgical management. Radiation and chemotherapy were recommended. She received 54 Gray of radiation to the tumor using intensity modulated technique (IMRT) and oral Temodar (temozolomide) chemotherapy for 42 consecutive days during radiation therapy at 90 mg/m² per day. The plan was to continue Temodar at 200 mg/m² x 5 days every 28 days, for 12 months.

At the current time, the patient remains stable and there has been no tumor progression five months after biopsy.

**DISCUSSION**

Children with AA have a poor prognosis (5-year relative survival rate of 23.6%) [3]. In 2014, Bechet et al., showed that a H3K27M mutation can be identified with high specificity and sensitivity with immune histochemistry (IHC) using a commercially available rabbit polyclonal antibody following biopsy [8]. When a H3K27M mutation is present, AA tends to progress in a similar fashion as diffuse intrinsic pontine glioma (DIPG). AA with these mutations and DIPG have a significantly worse prognosis (2-year relative survival rate of <10%) [9-12]. Both DIPG and midline gliomas present with limited surgical options and resistance to chemotherapy and radiation [12-14]. DIPG neuropathology is similar to that of anaplastic astrocytoma and often demonstrates somatic mutations in the histone H3 as well [10]. Within the H3 variant H3.3, the missense mutation G34R/V has also been identified in association with pediatric gliomas; however, unlike the H3K27M mutation, the H3.3G34R/V mutation is restricted to hemispheric tumors and thus offers a significantly better prognosis [15].

The effect of the H3K27 mutations is global reduction of tri-methylated histone H3K27 (H3K27me3). This is found in DIPG and is associated with all known H3K27 mutations [15]. Reduction of H3K27 methylation is characteristic of H3K27M mutant tumor cells and is not exhibited in wild-type H3.3 or H3.3G34R/V cells studied [16,17]. Reduced methylation has also been associated with the mutagenic substitutions H3.3K27I, H3.1K27M and H3.2K27M. These mutations have mostly been identified in DIPG [15]. Castel et al. first identified the mutagenic variants H3.3K27I, derived from the H3F3A gene, and H3.2K27M,
derived from the HIST2H3C gene, in a 2015 study where they each appeared, mutually exclusively, in only one patient[15]. However, H3.1K27M, derived from the gene HIST1H3B/C, and H3.3K27M, derived from H3F3, have been more widely studied and have shown distinct and predictable prognoses and phenotypes.

Although both mutations are associated with poor prognosis, H3.1K27M is associated with a slightly better prognosis than the H3.3K27M mutation. In the study conducted by Castel et al, H3.1 patients had a median overall survival length (OS) of 15.2 months compared to 9.2 for H3.3 patients, and 85% of H3.1 patients responded positively to therapy compared to 55.3% of H3.3 patients. Additionally, DIPG with the H3.3K27M-mutation exhibited a proneural/oligodendroglial phenotype with a pro-metastatic gene expression signature with PDGFRA (platelet-derived growth factor receptor alpha) activation, while H3.1K27M-mutated DIPG showed a mesenchymal/astrocytic phenotype and a pro-angiogenic/hypoxic signature [15]. Interestingly, despite carrying the H3.3 mutation, in our patient there was no amplification of PDGFRA and the tumor has demonstrated an astrocytic phenotype.

DIPG occurs almost exclusively in children and has a long-term (>2yr) survival rate of <10%[9-12]. For children with DIPG, there are limited therapeutic options due to minimal response to chemotherapy and radiation and surgical resection is impossible [12-14]. In a 2012 study comparing the outcomes of pediatric DIPG patients with and without the H3K27M mutation, there was a mean overall survival of 0.73 years following diagnosis for those with the mutation compared to 4.59 years for those without [18].

CONCLUSION

Since H3.3K27M can be identified with high specificity and sensitivity with immunohistochemistry (IHC) using a commercially available rabbit polyclonal antibody, children with biopsied or resected gliomas should be evaluated for this and other related histone mutations. Unfortunately, the prognosis for a child with a malignant glioma remains poor; however, given the distinct prognoses associated with various known tumorigenic histone mutations, knowledge of a specific mutation may significantly inform a course of treatment. Hopefully, further investigation of the tumorigenesis of the H3K27M mutation and the molecular mechanism by which these mutations contribute to malignancy will provide an opportunity to develop better treatment options for children with these tumors.

REFERENCES

Specific detection of methionine 27 mutation in histone 3 variants (H3K27M) in fixed tissue from high-grade astrocytomas. Acta Neuropathol. 2014; 128: 733-741


