A RARE CASE OF PEDIATRIC MN1 ALTERED ASTROBLASTOMA WITH CONCOMITANT ATM GERMLINE MUTATION

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Abstract

Astroblastoma is a rare brain tumor that has recently emerged as a new entity in the 2021 WHO classification of tumors of the central nervous system (CNS), based on its peculiar histopathologic feature and association with MN1 alteration. We report an unique case of MN1-altered astroblastoma with concomitant ATM germline mutation. A 10-year-old girl presented with nausea and vomiting due to a large temporal parietal tumor. Gross total resection was achieved and the integrated molecular diagnosis of MN1-altered astroblastoma was made based on DNA methylation profiling. Next-Generation Sequencing (NGS) confirmed a MN1-BEND2 fusion and germline sequencing revealed an ATM gene heterozygous pathogenic variant. Radiation therapy was deferred given the possible association of heterozygous ATM mutation with increased risk of breast cancer and radiosensitivity.

This case highlights the therapeutic implications of germline molecular findings in the treatment of astroblastoma and the need for further investigations to define a more standardized approach for treating this rare pediatric tumor.

Introduction:

Astroblastomas are rare neuroepithelial tumors that have emerged as a new entity in the 2021 World Health Organization (WHO) classification of tumors of the central nervous system (CNS), based on its peculiar histopathologic features of “astroblastic pseudorosettes” and Meningioma 1 (MNI) altered molecular characterization [1]. It comprises approximately 0.45%-2.8% of all glial tumors, with the majority affecting children, adolescents, young adults, and females disproportionately [2, 3]. Bailey and Cushing first introduced the term “astroblastoma” in 1926, with Bailey and Bucy further characterizing it through a series of 25 cases in 1930 [4, 5]. Its path to recognition as a discrete entity has been challenging given its rare occurrence, unknown origin, and clinical behavior, as well as overlapping features with astrocytomas and ependymomas [2, 6]. Astroblastomas tend to be well-circumscribed mass localized to the cerebral hemispheres though recent case reports have demonstrated its rare presentation in the spinal cord in the absence of MN1 alterations [7]. Astroblastic pseudorosettes are characterized by cuboidal or columnar cells with varying perivascular acellular regions, and vascular and perivascular hyalinization; features that can also be observed with other gliomas including anaplastic astrocytoma and glioblastoma [1-3, 8]. Therefore, prior to Strum and colleagues discovery of CNS high-grade neuroepithelial tumor with MN1 alteration (CNS HGNET-MN1) as a new entity based on modern DNA methylation profiling of primitive neuroectodermal tumors of the CNS in 2016, astroblastomas were previously included under the category of “other gliomas” in the 2016 WHO classification of tumors of the CNS [9]. Currently, no clear histological features for grading astroblastomas have been defined but they can be broadly categorized into low-grade and high-grade with the latter fulfilling the following parameters: increased cellularity, anaplastic nuclear pattern, high mycotic index (> 5/10 high power fields), vascular proliferation, necrosis with pseudopalisades, and MIB-1 proliferative index between 6
and 22% [10].

Herein, we report a case of a 10-year-old girl with MN1 -altered astroblastoma who interestingly also harbor an ataxia-telangiectasia mutated (ATM) mutation discovered upon genome sequencing.

**Case Presentation:**

A 10-year-old female presented with 3 weeks of progressively worsening nausea and vomiting was found to have a large complex partially solid, partially cystic intra-axial mass in the left temporal parietal lobe with internal calcifications and mild mass effect on computed tomography (CT), concerning for primary brain tumor.

Neurological examination demonstrated right-sided pronator drift but was otherwise unremarkable. Magnetic resonance imaging (MRI) revealed a left temporal parietal cortically based cystic lesion with a solid enhancing component with surrounding vasogenic edema (Fig A-B).

The patient underwent craniotomy for gross total resection. Histopathological analysis revealed a highly cellular spindle cell tumor with brisk mitotic activity, positive immunohistochemical staining for Olig2 and ATRX, and negative for GFAP (Fig C-F). DNA methylation profiling was consistent with a diagnosis of CNS high grade neuroepithelial tumor with MN1 alteration, confirmed on Next-Generation Sequencing (NGS) as a MN1-BEND2 fusion. Germline sequencing demonstrated an ATM heterozygous pathogenic variant (ATM c.103C>T). The patient remains disease free 8 months after diagnosis in the absence of adjuvant therapy.

**Discussion:**

Astroblastoma is a rare entity with limited reports in existing literature. Ahmed et al. reported a median overall survival (OS) of 55 months, with the 1-, 5-, and 10-year OS reported 71.1%, 48.5%, and 38.3% respectively in the largest report of astroblastoma patients [11]. Currently, no standard of care exists for astroblastoma as the clinical behavior and prognostic criteria for the disease entity remains unpredictable, largely owing to its molecular heterogeneity. Current treatment of choice for astroblastoma consists of gross total resection with adjuvant radiotherapy frequently performed in cases of high-grade tumors but with variable response [10]. The use of adjuvant chemotherapy such as temozolomide has been described but remains controversial [10].

In the current case, the patient was diagnosed with high-grade MN1 altered astroblastoma based on histopathological findings and methylation profile. Initial consideration was given regarding the possible administration of adjuvant radiotherapy given the high proliferation index (a Ki-67 labeling index of approximately 80%). However, given the germline ATM gene heterozygous stop-gain variant, radiation therapy was deferred since the ATM gene product is implicated in the DNA damage recognition pathway, signaling in response to DNA double-strand breaks and oxidative stress, as well as activating cell cycle checkpoints [12]. Whereas ataxia-telangiectasia is a well-known autosomal recessive condition of the ATM gene predisposing affected individuals to higher risks of developing childhood leukemia and lymphoma, carriers of the gene are also said to have increased propensity for developing breast cancer, as well as possible radiosensitivity [12, 13]. To the best of our knowledge, this is the first case of MN1 -altered astroblastoma with concomitant ATM germline mutation to be reported and the implication of adjuvant radiotherapy remains unknown. Our case adds to molecular heterogeneity of MN1 -altered astroblastoma, highlighting the importance of DNA methylation and germline sequencing in the diagnosis and management of this rare pediatric tumor type.

**References**


**Figure legend**

**Astroblastoma MN1 altered Neuroradiographic and Neuropathologic Features**

T2-weighted MRI reveals a large temporal parietal cystic tumor associated with surrounding vasogenic edema (A) and rim enhancement on post-gadolinium weighted sequences (B). Microscopic sections show a highly cellular spindle cell tumor with brisk mitotic activity (C). The tumor cells demonstrated absent immunohistochemical reactivity for GFAP (D) and positivity for Olig2, and (E) ATRX (F) (C-F: magnification x200).