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Case Report

Histopathologically atypical astroblastoma with MN1-CXXC5 fusion transcript diagnosed by methylation classifier

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Abstract

Adult astroblastoma is an exceedingly rare primary brain tumor. Previous reports have suggested various radiographic and histological features typical for these tumors, but the diagnosis can be challenging. We present a unique case of astroblastoma diagnosed after 13 years of treatment as a CNS embryonal neoplasm. Histologically, this tumor lacked previously identified astroblastic features such as pseudorosettes, trabeculated patterns, and hyalinized vessels. The tumor was synaptophysin positive which further confounded the diagnosis in this case. Methylation classification was performed with a high confidence match to a high-grade neuroepithelial neoplasm with a CXXC5-MN1 fusion. Molecular characterization confirmed a CXX5-MN1 fusion transcript which has been seen in at least one other instance. Though known to be involved in tumorigenesis, the roles of CXXC5 and MN1, in this case, remain unclear. We discuss the unusual histopathological features of this tumor and the value of recent updates to the WHO molecular diagnosis scheme for central nervous system tumors. We also briefly review the literature related to astroblastoma. The current case highlights our evolving recognition of atypical histological patterns for astroblastoma and the importance of new molecular profiles which can aid in the diagnosis.

Case

The patient is a 36-year-old woman who presents in 2007 with intractable headache plus nausea and vomiting. A left mesial parietal mass was identified by MRI and subsequently resected. The preliminary pathology was unclear, but the tumor was classified as a Primitive Neuroectodermal Tumor (PNET), WHO grade 4. Her postoperative course was complicated by wound site infection that delayed subsequent radiation and chemotherapy and which ultimately required another surgery for washout. After the resolution of her infection, she received craniospinal radiation followed by temozolomide, etoposide, carboplatin and cyclophosphamide. The first radiographic recurrence occurred 5 years after the initial presentation. She underwent a second resection to debulk and clarify the diagnosis, but the histological classification remained unclear. A provisional diagnosis of CNS embryonal type neoplasm was made, and a gross total resection was achieved. Post-operatively, she was treated with bevacizumab and carboplatin. Subsequently, she underwent induction chemotherapy with carboplatin, etoposide, and thiotepa followed by an autologous stem cell transplant. The course was again complicated by chronic craniotomy site wound infection which required definitive craniectomy and cranioplasty with a titanium plate. At this time, her primary deficits were cognitive and attributable to craniospinal radiation.

She developed a second radiographic recurrence in 2021 (Figure 1). Given the refractory nature of the tumor, and given the unclear histological diagnosis, she underwent a third surgery with the goal of making a definitive diagnosis and debulking the tumor. Histological features were similar to previous resections (Figure 2). Her tumor was sent for methylome profiling followed by next-generation sequencing which disclosed a CXXC5-MN1 fusion transcript. Based on accumulated methylome data and recent updates to WHO

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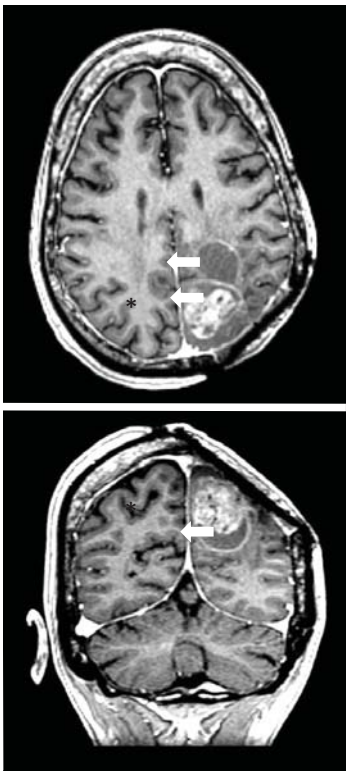

Figure 1: Gadolinium-enhanced MR imaging from 2021 of the recurrent astroblastoma from our patient. Evidence of 2 prior resections includes cystic cavities (arrows) into which the tumor is growing from the posterior medial aspect of the largest cavity. As with other cases of astroblastoma, there are bubbly features (asterisk) of recurrent enhancing tumor and minimal associated edema.

classifications of primary tumors, the MN1 fusion, and methylome profile confirmed diagnosis of Astroblastoma, MN-1 altered, WHO Grade 4 (Louis 2021). No other actionable mutations were discovered by sequencing using a 170 gene in-house screening assay or with Foundation Medicine CDx testing. Surgery was followed by concurrent radiation/temozolomide followed by 6 cycles of adjuvant temozolomide. At last encounter, she had symptoms of cognitive slowing and a 6-month history of subacute progressive ataxia and length-dependent peripheral neuropathy. While it is tempting to blame her symptoms on previous therapy, she was found to have thiamine deficiency due to self-imposed dietary restrictions to which ataxia and neuropathy may be attributable.

Evidence of 2 prior resections includes cystic cavities (arrows) into which the tumor is growing from the posterior medial aspect of the largest cavity. As with other cases of astroblastoma, there are bubbly features (asterisk) of recurrent enhancing tumor and minimal associated edema.

Discussion

Only a handful of astroblastomas have been reported that share the CXXC5-MN1 fusion, and none with the atypical histological features of the current case [1-3]. The current case highlights the importance of methylation profiling in diagnosing primary brain tumors. The new WHO diagnostic criteria based on methylation profiling [4] have led to other astroblastoma diagnoses with CXXC5-MN1 fusions [3,5].

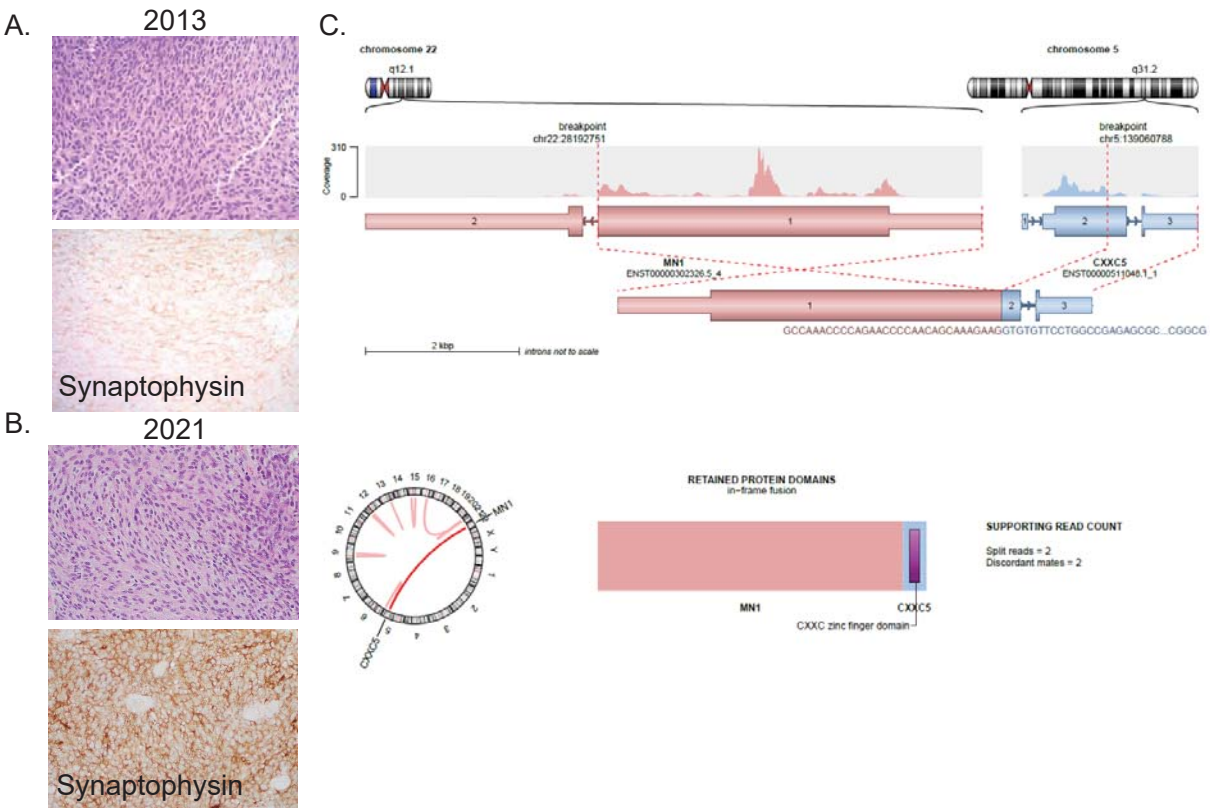

Figure 2: Histopathological findings from 2013 (A) and 2021 (B). H&E and IHC from 2013 showed a small blue cell tumor consistent with high-grade embryonal neoplasm, possibly PNET (A). Morphology and synaptophysin expression are unchanged; lab changes in reagent account for intensity differences in synaptophysin. (B). Schematic of the CXXC5-MN1 fusion protein as suggested by methylation and confirmed by molecular sequencing (C).

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Radiographic imaging was non-specific (Figure 1) and histopathology from both earlier and later resections failed to generate a clear diagnosis (Figure 2). Purported histological hallmarks of astroblastoma are radially arrayed neoplastic cells with papillary or pseudopapillary formations in ribbon-like/trabecular alignment called astroblastic pseudorosettes [1,3,6-9]. The tumor in this case had no rosettes, papillary or pseudopapillary features, nor trabeculae. Instead, there were vague streams and nests of cells with round mildly pleomorphic nuclei. Features of high-grade embryonal neoplasm were also present, including high mitotic rate, anaplastic morphology, high cellularity with cellular atypia, and endothelial hyperplasia without vessel wall sclerosis [10]. Moreover, extensive synaptophysin staining is unusual in astroblastoma and further obscured the final diagnosis. The most recent pathologic sample from the 2021 resection showed up to 5 mitoses in a single high-powered field, Ki-67 of 35%, high cellularity with atypia, and anaplastic features. Endothelial hyperplasia was absent. Only methylome-based profiling and sequencing which found meningioma 1 (MN1)-CXXC5 fusion transcript allowed the diagnosis of astroblastoma [4,8].

The function of MN1 in astroblastoma and other solid tumors is unknown. However, the oncogenic role of MN1 overexpression has been confirmed in AML [11]. Elevated MN1 protein levels strongly correlate with chemotherapy resistance and confer a poor prognosis among these patients [11-19]. Oncogenic MN1 depends upon poly-glutamine stretches, particularly at the N-terminal region, and SMARCA4 to stabilize BAF-chromatin binding [11]. The BAF complex mediates ATP-dependent nucleosome remodeling and maintains the active state of enhancer regions [20-22]. MN1-knockout mouse models exhibit neonatal lethal palatal abnormalities [23]. Similar features are seen in infants with MN1 C-terminal truncation syndrome which is phenotypically characterized by craniofacial malformations and impaired rhombencephalon formation [24].

MN1 amplification is associated with meningioma, astroblastoma, and particularly with acute myeloid leukemia (AML) where it influences the prognosis for patients with MN1 alterations [7,13-15,25,26]. Increased expression of MN1 in patients with AML and the otherwise normal karyotype is associated with shorter survival and reduced response to treatments [13]. However, the role of MN1 alterations in astroblastoma remains unclear. The CXXC5 gene codes for a transcriptional regulator which is ubiquitously expressed and connected to a number of human neoplasms [27-31]. It is a member of the CXXC-type zinc-finger protein family. CXXC5 activation appears to negatively feedback against the WNT/β-catenin pathway, regulating glucose metabolism [32]. Though seen here and in other cases of astroblastoma, it is unclear how the CXXC5-MN1 fusion affects astroblastoma survival. Equally unclear is whether the fusion product has prognostic significance in addition to the known diagnostic significance.

Radiographically, astroblastomas appear well demarcated with a "bubbly" appearance due to signal voids caused by atypical vascular architecture on MRI [33,34]. There may be minimal perilesional edema relative to their large size which may be related to the non-infiltrating nature of these tumors and the (generally) slow growth. They are hyperintense on T2-weighted imaging and hypo- to isointense on T1. Imaging was not available from the time of diagnosis in 2007. However, subsequent recurrences were radiographically consistent with previous publications. Radiographic features are highly non-specific, and in this case, they were confounded by previous resections.

The lack of clarity regarding the diagnosis and prognosis of astroblastoma, particularly among adults, directly relates to the rarity of the diagnosis. It is among the rarest adult primary neoplasms accounting for fewer than 3% of all diagnosed neurologic tumors. The actual incidence of astroblastoma based on a broad literature review has been estimated at 1.6 new patients/per year [35]. These tumors have a predilection for women over men with a reported male-to-female ratio ranging from 1:1.7 to as high as 1:11 [35,36]. Symptoms suggesting tumor growth depend upon anatomic location but may also be non-specific for patients who present first with headaches. The current case fits neatly into this epidemiological pattern, though at 36, our patient was in the upper age range for adults diagnosed with astroblastoma. Age at diagnosis with astroblastoma is generally bimodal with peaks in the first and third decades of life; however, MN1 alterations are mostly seen among patients diagnosed under 10 years of age [2]. While it is tempting to hypothesize various mechanisms for tumorigenesis on the basis of MN1 genetic and epigenetic regulation, it may simply be that we have an incomplete understanding of MN1 alterations in astroblastoma. Indeed, the sub-classification of astroblastoma continues to evolve. It is unclear whether MN1, CXXC5, or other genes (such as BEND1 or EWSR1) may be most influential in these tumors.

Regardless of age at diagnosis, surgery remains the mainstay of treatment for astroblastoma. A large national cancer database was unable to show significant increases in overall survival relating to post-operative radiation and/or chemotherapy, but there was a trend suggesting benefits for patients who had tumors with high-grade features [37]. Our patient has survived > 14 years since initial treatment in 2007 following aggressive maximal safe resection and craniospinal radiation (at that time for presumed high-grade PNET). Our patient also received multiple rounds of chemotherapy even up to ablative chemotherapy requiring a stem cell transplant. While the current case is insufficient to support the use of any particular therapy, treatment with platinum-based therapy and etoposide is common when dealing with embryonal-type tumors. Given the intensity of prior chemotherapies used in this case and based on the lack of efficacy data for particular regimens for recurrent astroblastomas, we chose temozolomide for its well-known efficacy against various types of intracranial neoplasms and low toxicity profile. Prognosis is generally favorable for astroblastoma. Overall survival for patients with astroblastoma is approximately 80% after 5 years and may be better than 60% at 10 years [37]. Data are lacking for long-term survival at recurrence.

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Conclusion

The current case is unique histologically for the presence of synaptophysin in astroblastoma without other typical features. Moreover, this case highlights the value of recent advances in methylome based tumor profiling which accurately identifies MN1-altered astroblastoma.

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