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Case Report

Recurrent HGNET-MN1 altered (astroblastoma MN1-altered) of the foramen magnum: Case report and molecular classification

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ABSTRACT

Background: Astroblastoma is a rare primary brain tumor of unclear origin, often occurring in young patients less than 30-years-old. It typically arises supratentorially and is diagnosed based on histological features including vascular hyalinization and perivascular pseudorosettes. Recent molecular characterization of primary CNS high-grade neuroepithelial tumors with meningioma I alteration (HGNET-*MN1*) found that HGNET-*MN1* and tumors with morphological signatures of astroblastoma clustered together. Further analysis revealed such astroblastomas have *MN1* alteration and the 2021 WHO classification of tumors of the CNS now recognizes astroblastoma *MN1*-altered as a new entity.

Case Description: Here, we present the case of a 36-year-old right-handed woman with recurrent low-grade astroblastoma in the cervicomedullary junction. The patient presented with worsening motor and sensory deficits of her upper extremities, pain, ataxia, visual disturbance, and nausea. Due to extensive recurrence and neurological symptoms, the patient underwent reoperation.

Conclusion: We review a rare case of recurrent astroblastoma in the foramen magnum in light of new relevant literature about tumor biology and prognostic significance of the new classification of astroblastoma *MN1*-altered.

Keywords: Astroblastoma, *MN1*-altered, Foramen magnum

INTRODUCTION

Astroblastoma located in the cervicomedullary junction is an exceedingly rare entity.[9] Recent molecular analysis discovered a subset of CNS primitive neuroectodermal tumors classified as astroblastoma based on morphology, molecularly clustered with CNS high-grade neuroepithelial tumor with *Meningioma 1* alteration (HGNET-*MN1*).[14] The 2021 WHO classification of tumors of the CNS and 2020 c-IMPACT-NOW 6c recognizes a new entity entitled astroblastoma *MN1*-altered based on a combination of this molecular change and morphological features of astroblastoma.[6,7] Here, we present a case of recurrent astroblastoma *MN1*-altered affecting the foramen magnum and discuss recent changes to the molecular classification of such tumors.

CASE PRESENTATION

A 36-year-old right-handed woman with a history of low-grade astroblastoma presented with a 2-month history of worsening left-sided weakness, neck pain, right upper extremity numbness, gait ataxia, blurry vision, nausea, dizziness, and fatigue. She previously underwent gross total surgical resection in 2002 followed by 6 weeks of radiation therapy in 2004 for progressive disease. Tumor progression in 2015 prompted subtotal resection followed by hypofractionated stereotactic radiosurgery for continued progression in 2016 and six cycles of temozolomide in 2017. The patient has a long-standing history of orthostatic hypotension, back pain, spasticity, and left foot drop.

On physical examination, the patient had persistent horizontal nystagmus on bilateral lateral gaze, tongue deviation to the right, and left-sided hemiparesis. Upper and lower extremities were spastic bilaterally but worse on the left side. Lower extremities were deconditioned with 0/5 motor strength in the left ankle, which was hyper-reflexic with nonsustained clonus. Fine touch sensation was diminished in the right upper extremity and proprioception was diminished in the right upper extremity and both lower extremities.

MRI imaging revealed a right paramedian intradural foramen magnum lesion, most likely representing recurrent expansile cervicomedullary astroblastoma given the patient's history [Figure 1a-c]. The expanded differential included astrocytoma, ependymoma, DNET, lymphoma, ganglioglioma, subependymoma, metastasis, lower cranial nerve schwannoma, or granuloma.

The patient was considered a candidate for repeat surgical resection using a midline sub-occipital approach with the patient in the prone position to avoid the prior right far lateral craniotomy. A sub-occipital craniotomy, C1 laminectomy, midline durotomy, and subtonsillar approach were used. Neuromonitoring, SSEPs, and MEPs for cranial nerves 9, 10, 11, and 12 were utilized with the goal of maximal safe debulking using ultrasound, the operative microscope, and neuronavigation. Tissue samples were obtained for histological and immunohistochemical analyzes.

The patient tolerated surgery well and was extubated. Postoperatively, she experienced bilateral numbness in all extremities with increased numbness on the right side. Baseline left-sided hemiparesis and bilateral hyper-reflexia remained. Muscle tone in the upper and lower extremities was increased without spasticity and tongue deviation was further to the right. Postoperative MRI demonstrated successful resection of the lesion [Figure 1d-f]. Ultimately, the patient was ambulatory with assistance and transferred to the inpatient rehabilitation service on postoperative day 5.

Pathological analysis revealed an epithelioid neoplasm with tumor cells displaying elevated mitotic activity with a

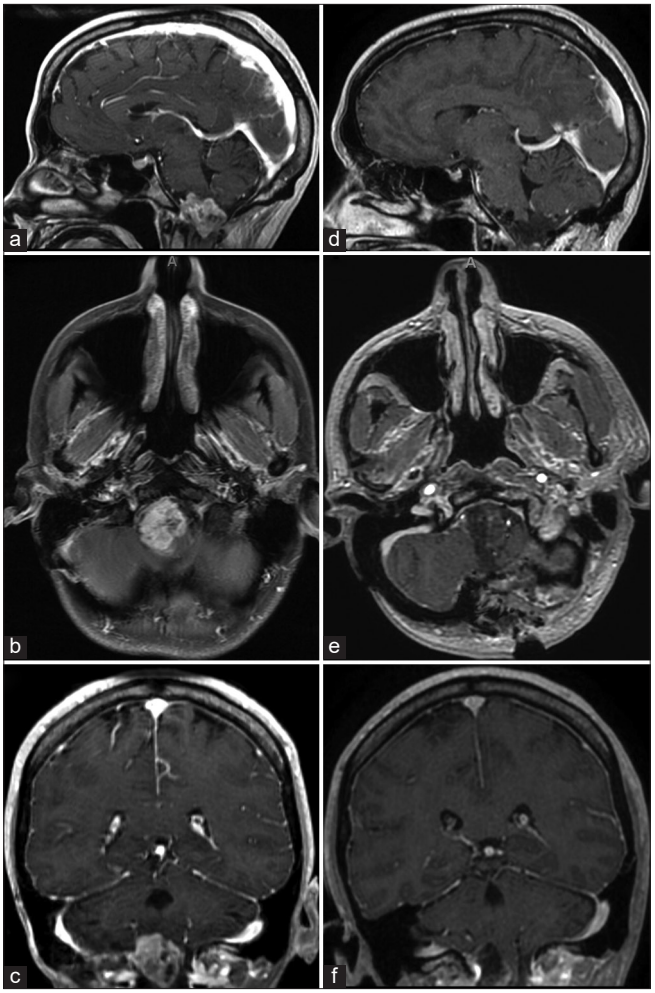

Figure 1: MRI of astroblastoma MN1-altered tumor. (a-c) Sagittal, axial, and coronal preoperative T1 MRI revealing an intra-axial, heterogeneously enhancing lesion centered in the cervicomedullary junction with rostral extension into the pontomedullary junction and caudal extension into the C1-C2 spinal cord. (d-f) Sagittal, axial, and coronal postoperative T1 MRI demonstrating successful resection of the lesion.

Ki67 proliferation index of 19% on average and up to 26% in hotspots, distinct cell borders, and variable sheet-like, pseudopapillary, and trabecular architecture [Figure 2a-c]. Multiple foci of bland necrosis with hyalinized vessels were also found, consistent with history of radiation treatment. Immunoreactivity for glial fibrillary acidic protein and epithelial membrane agent was both positive [Figure 2d and e]. Tumor histopathology was consistent with recurrent astroblastoma and molecular classification allowed for further specific diagnosis as CNS HGNET with features of MN1-altered astroblastoma morphology.

At 15-month follow-up, the patient had completed four cycles of bevacizumab and lomustine but continued to decline with worsening diffuse weakness and quadriplegia

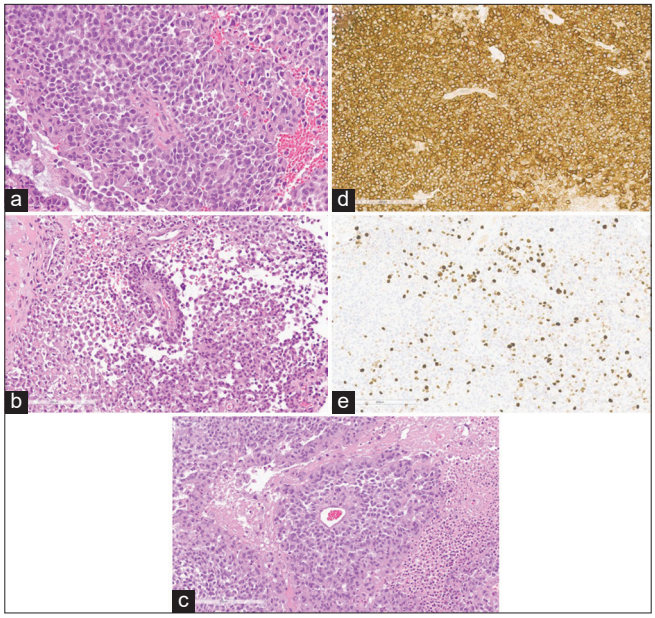

Figure 2: Histopathology of astroblastoma MN1-altered tumor. (a-c) Hematoxylin and eosin staining exhibiting epithelioid neoplasm with highly mitotic tumor cells with an average Ki67 proliferation index of 19%, distinct cell borders, variable sheet-like, pseudopapillary, and trabecular architecture, and multiple foci of bland necrosis with hyalinized vessels. (d) Positive for EMA immunoreactivity, (e) positive for Ki67 staining (average index of 19%, hotspots of 26%).

due to tumor recurrence. The patient required frequent assistance and medical care with a Karnofsky performance score of 50. Given her progressive decline with worsening weakness and quadriplegia, patient was referred to home hospice.

DISCUSSION

Background

Astroblastoma is a rarely occurring glioma estimated to account for 0.5–2.8% of diagnosed pediatric gliomas.[9] These tumors occur more frequently in females and have bimodal peaks of incidence at approximately 5–10 years of age and 21–30 years of age.[15] Over 80% of astroblastomas occur in the supratentorial compartment.[15] Astroblastomas are rarely found in the brainstem or spinal cord with < 5% of tumors occurring in this area with few documented cases.[3,10,12,13,15-17,19] Here, we present a patient with recurrent astroblastoma *MN1*-altered at the foramen magnum. This female patient with initial diagnosis of astroblastoma at age 19 falls into the expected demographic. Historically, recurrence of astroblastoma is not uncommon.[8] With most documented cases originating supratentorially, the location of this tumor in the cervicomedullary junction is unique.

Histologic and genetic characteristics of astroblastoma

Given the rarity of astroblastoma, ependymoma typically needs to be excluded, especially since both tumors frequently occur in younger patients and appear well-circumscribed, solid, and cystic.[1] However, ependymoma lacks the perivascular hyalinization seen with astroblastoma.[4,11] Vascular hyalinization and extensive perivascular pseudorosettes with thickened, stout, or non-tapering cell processes and hyalinization are key features critical for diagnosis,[4,18] Astroblastoma is typically positive for Olig2 and negative for IDH1-R132H mutation, EGFR mutation, loss of chromosome 10, gain of chromosome 7, and other common genetic alterations found in glioblastoma.[4] In a recently published series of astroblastoma cases, MGMT promoter hypermethylation was present in only 12% and 38% of 21 cases were BRAF V600E mutated.[4]

Molecular analysis has allowed for classification of primitive neuroectodermal tumors of the CNS and has given rise to four novel brain tumor groups defined by DNA-methylation, including a new entity termed CNS HGNET-*MN1* located at 22q12.3.[14] From the molecular analysis performed in the study, 41 tumors were reclassified into this group, 16 (39%) of which showed histological features of astroblastoma with dense, pericellular hyalinization, and pseudorosettes.[14]

Prognostic factors and new classification

Given this new discovery, a series of cases with either astroblastoma morphology or molecular *MN1* alteration were reanalyzed for prognostic significance. In a case series of 73 patients with *MN1* altered tumors, astroblastoma morphology was significantly associated with improved overall survival compared to nonastroblastoma tumors, suggesting the value of an integrated molecular and histological diagnosis.[2] In another case series of 27 patients with histologically-defined astroblastoma, ten cases with MN1 alteration were found to have better overall survival, especially when compared to BRAFV600E mutated tumors.[5] These preliminary studies indicate that astroblastoma with *MN1*-alteration harbors the greatest survival benefit within both the genetic variants of morphological astroblastomas and morphological variants of CNS HGNET-*MN1*. This was reflected in the decision of the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy-Not Official WHO (c-IMPACT-NOW) update 6c in 2020 to recognize a new tumor called astroblastoma, *MN1* altered.[7] Astroblastoma *MN1*-altered was officially added to the 2021 WHO classification of tumors of the CNS as well.[6]

Molecular considerations

Interestingly, recent reports of brainstem and spinal cord astroblastoma tumors have a novel fusion between Ewing

sarcoma breakpoint region 1/EWS RNA binding protein 1 (EWSR1) and BEN Domain Containing 2 (BEND2).[13,17] The original report that established the molecular characteristics of astroblastoma, *MN1* altered included a MN1-BEND2 fusion,[14] and this novel EWSR1 fusion appears to hold similar methylation patterns to the MN1-BEND2 fusion.[17] While our case lacked such a fusion, it indicates that spinal astroblastoma may hold other unique fusions that should be further studied.

The histologic and clinical features of our patient's neoplasm are consistent with the newly described astroblastoma *MN1*-altered, specifically a recurrent HGNET-*MN1* altered astroblastoma. In addition, another recent molecular case series which reanalyzed previously diagnosed astroblastomas observed that *MN1*-altered tumors had a prolonged clinical course with multiple local tumor recurrences, which was also seen in our case.[5,18] Because astroblastoma histology is not specific, additional genetic characterization now allows for improved classification using genetic alterations and methylation profiles, which provide valuable prognostic information.[18] Since the majority of CNS-HGNET, *MN1* cases lacked characteristic astroblastoma morphology, it is possible that astroblastoma is a morphologic pattern that can be observed across various molecularly-defined tumors.[5,18]

CONCLUSION

Foramen magnum tumors may be challenging to localize due to myriad of symptoms that cause complex clinical presentation. Astroblastomas have characteristics of both astrocytoma and ependymoma, though its origin remains unclear.[4] While clinical outcomes of these tumors are variable, aggressive tumor resection contributes to prolonged overall survival.[19] Due to the rarity of the disease, adjuvant therapy regimens for patients with incompletely resected tumors include radiation, TMZ, and bevacizumab.[19] The recent WHO classification of astroblastoma, *MN1*-altered fits the characteristics of our patient's tumor and holds prognostic significance.[2,5-7]While the 2021 WHO classification did not assign tumor grade, genomic analysis classifies most astroblastomas into HGNET (*MN1* altered), high-grade astrocytoma (PTEN mt), or unclassified (p53 mt).[5,6,14,18] Ultimately, astroblastoma represents a morphologic and histologic entity of genetically distinct tumor types.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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