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SHORT COMMUNICATION

RBM10 truncation in astroblastoma in a patient with history of mandibular ameloblastoma: A case report

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Abstract

Astroblastoma is a rare glial neoplasm composed of cells that have broad processes oriented perpendicular to central vessels and often demonstrate vascular sclerosis. The WHO 2016 classification does not specify a grading system for astroblastoma, and categorizes them as well-differentiated or malignant. These broad classification rubrics, however, do not accurately predict clinical outcome. Genetic profiling of astroblastoma has therefore been of particular interest in the recent years. These efforts, although in small number, have revealed heterogeneous molecular findings that may explain astroblastoma's unpredictable clinical outcome. Here, we report a case of recurrent astroblastoma in a 23-year-old female with a unique molecular characteristic. Our patient's tumor harbored an RNA-binding motif 10 (*RBM10*) truncation. *RBM10* codes for a widely expressed RNA binding protein, and its mutation has been described in a variety of solid cancers. *RBM10* is thought to be involved in stabilization of pro-apoptotic proteins in breast cancer, and its reduced protein expression is associated with advanced stages of lung adenocarcinoma. To our knowledge, this is the first report of astroblastoma harboring *RBM10* truncation. Interestingly, our patient also has a history of mandibular ameloblastoma, but the link between these two rare tumors is unclear.

Keywords Astroblastoma, RBM10, Ameloblastoma, Genetic profiling, Glial neoplasm.
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Case description

Patient is a 23-year-old right-handed female with a history of resected ameloblastoma of the left mandible four years prior, who developed progressive headaches and visual impairment. Magnetic Resonance Imaging (MRI) of the brain showed a large left frontal lobe cystic mass with homogenous contrast enhancement in the periphery and central necrosis (Fig. 1(A) and (B)). She underwent gross total resection (Fig. 1(C) and (D)), and pathology revealed astroblastoma with classic findings of astroblastomatous perivascular pseudorosettes (Fig. 2(A)) and collagenous vascular sclerosis (Fig. 2(B)). Her symptoms resolved, and for the subsequent two years she was followed by serial imaging. She then experienced tumor progression, with her brain MRI showing interval increase in the size of the contrast-enhancing component inferior to the left frontal cyst (Fig. 1(F) and (G)). She underwent repeat resection, and pathology confirmed recurrent astroblastoma. She presented to our center one month after surgery, where her diagnosis of recurrent astroblastoma was confirmed. Histologically, cells were positive for GFAP and negative for Neu N. Ki-67 index was 19.3%, suggestive of aggressive biological behavior. MRI of the spine was negative for leptomeningeal dissemination, and cerebrospinal fluid cytology did not identify malignant cells. She underwent proton radiation to a total dose of 59.7 cGy in 33 fractions. She was then started on adjuvant standard dose temozolomide. She has currently completed 6 cycles of temozolomide with

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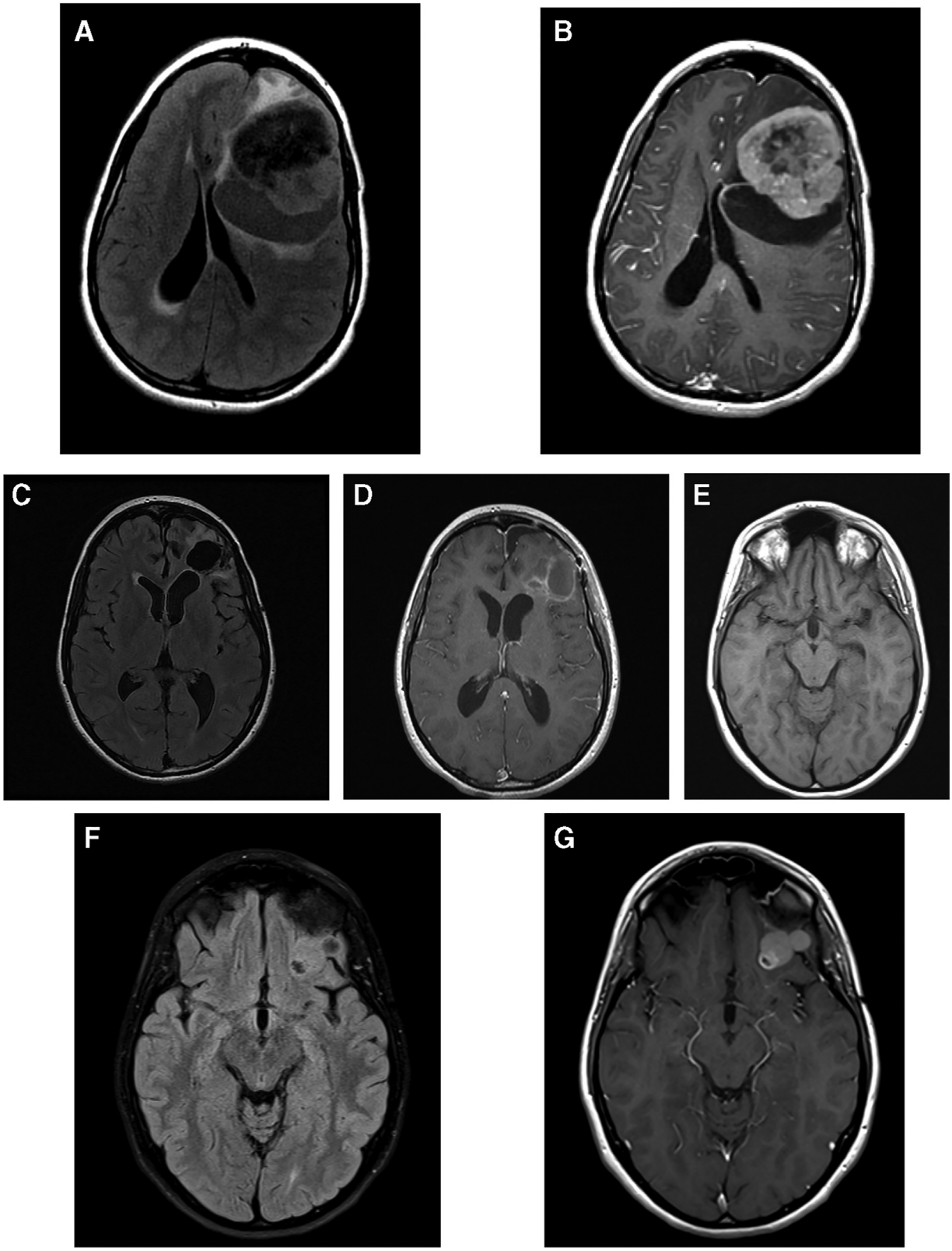

Fig. 1 Magnetic resonance imaging (MRI) sequences of left frontal astroblastoma at the time of initial diagnosis and recurrence. T2-FLAIR and T1-post-contrast images of the initial tumor demonstrates a homogenously contrast-enhancing tumor with central necrosis and a cystic component posteriorly (A&B). T2-FLAIR, T1-post-contrast images 4 months after tumor resection (C&D). T1-post-contrast image after first resection at a lower level where recurrence occurred about 15 months later (E). T2-FLAIR and T1-post-contrast images demonstrating multicystic contrast-enhancing growth inferior to the prior resection cavity (F&G).

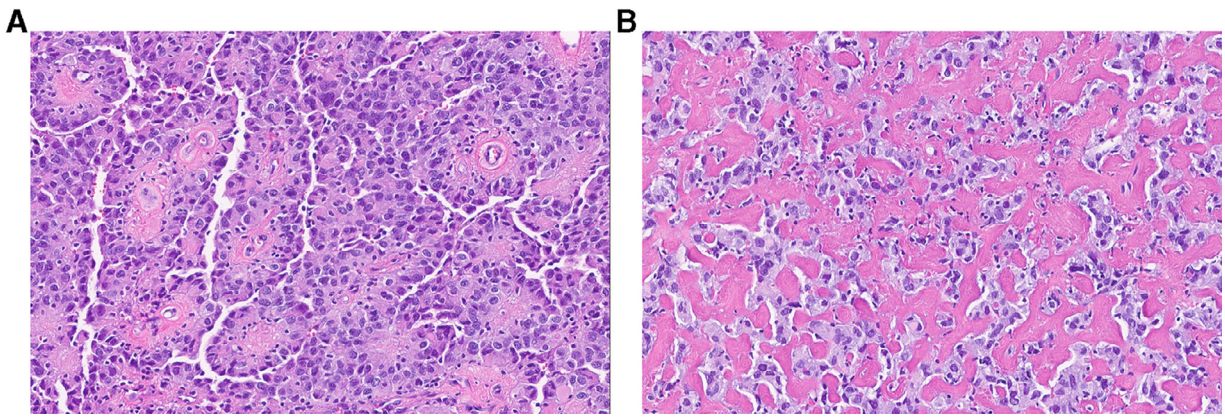

Fig. 2 Haemotoxylin and Eosin (H&E) staining of tissue obtained at the time of initial diagnosis. Area of dense cellularity and abundant area of classical astroblastomatous perivascular pseudorosettes (A). Area of low cellularity with dense vascular collagenous sclerosis characteristic of astroblastoma (B).

good tolerance and stable MR imaging. Genomic profiling via the FoundationOne® platform revealed an RNA-binding motif 10 (*RBM10*) truncation in her recurrent tumor. At the time of this analysis, FoundationOne® interrogated 315 genes, as well as introns of 28 genes involved in rearrangements. There were no alterations in genes commonly altered in infiltrating gliomas (*IDH1, IDH2, ATRX, and TP53*) or circumscribed glial neoplasms [1]. Interestingly, this is the first case of an astroblastoma in a young patient with history of ameloblastoma [2] and has been previously reported by King and colleagues from the University of Mississippi Medical Center. They raised the possibility of nevoid basal cell carcinoma syndrome [3] in a young adult given the co-occurrence of these two rare primary tumors. However, the patient's serum was tested for PTCH1 gene and a mutation was not detected. *RBM10* mutation in her ameloblastoma has not been tested and the link between these two rare tumors in this young individual remains unclear.

Discussion

Astroblastoma is a rare CNS neoplasm composed of cells that are positive for GFAP and have broad, non- or slightly-tapering processes radiating towards central blood vessels that often demonstrate sclerosis according to the WHO 2016 classification [4]. These tumors are traditionally thought to be glial neoplasms, given the GFAP positive staining and lack of neuronal or ependymal differentiation. More recently, tanycytes, cells with intermediate features between astrocytes and ependymal cells, have been suggested as the cells of origin in astroblastomas, based on ultrastructural observations [5,6]. Definitive epidemiologic data regarding astroblastoma is not available due to lack of uniform diagnostic criteria and rarity of the tumor. The WHO 2016 classification does not specify a particular grading system for this tumor, and categorizes them as well differentiated or malignant based on cellularity, mitotic activity and presence or absence of anaplastic nuclear features and necrosis [4,7]. These broad categorizations were once thought to be predictors of clinical outcome [8], but this association has been challenged by more recent case reports and epidemiologic studies [9–11] . The rarity of this tumor may in part be due to misdiagnosis due to poorly-defined histological features [11,12]. Pathological diagnosis of astroblastoma has been questioned with the more recent DNA methylation profiling and targeted next generation sequencing that suggest reclassification of these tumors into more specific molecular entities [11,13]. Therefore, molecular characterization of astroblastoma is crucial in our efforts to achieve more uniform diagnosis, establish prognosis, and discover targeted therapies.

Studies reporting molecular aberrations in astroblastomas using modern techniques are scarce. In one study involving 28 astroblastomas, 39% were found to have BRAF-V600E mutations using a single nucleotide extension assay [14]. One next generation sequencing study of 3 cases found alterations in genes that are known to be presented in low grade gliomas including BCOR, BCORL1, ERBB3, MYB and ATM, but no recurrent mutations were seen [12]. DNA methylation profiling of 323 primitive neuroectodermal tumors of the CNS identified four new molecular entities, including "CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2)," "CNS Ewing sarcoma family tumor with CIC alteration (CNS EFT-CIC)," "CNS high-grade neuroepithelial tumor with MN1 alteration (CNS HGNET-MN1)," and "CNS high-grade neuroepithelial tumor with BCOR alteration (CNS HGNET-BCOR)". Interestingly, 39% of the CNS HGNET-MN1 tumors showed histological features of astroblastoma [13]. Within the CNS HGNET-MN1 entity, interchromosomal gene fusions between MN1 and BEND2 (BEN domain containing 2) and MN1 and CXXC5 (CXXC-type zinc finger protein 5) were identified. High level gene expression of MN1-BEND2 was seen in CNS HGNET-MN1 tumors, while being absent in other CNS tumor types. Tumors containing MN1-BEND2 and MN1-CXXC5 fusions belonged to distinct clusters potentially indicating that each fusion partner determines the underlying pathology. These findings raised additional interest in identifying the *MN1* locus and specific methylation profile of astroblastoma. Wood and colleagues performed next generation sequencing of 500 cancer-associated genes in 8 astroblastoma cases and correlated them to FISH analysis of the *MN1* locus and genome-wide DNA methylation profiling. Out of 8 cases, only 3 grouped with the CNS-HGNET-MN1 entity. Out of the four MN1-intact cases, 2 with the most aggressive clinical course were thought to be misdiagnosed; one showed molecular

features of anaplastic pleomorphic xanthoastrocytoma, and one showed molecular features consistent with IDH-wildtype glioblastoma. The authors suggested that astroblastoma histology may not be specific for any entity, including CNS-HGNET-MN1, and that astroblastomas should be classified into more specifically-defined molecular subgroups [11]. Interestingly, one recent publication identified MN1-BEND2 fusion acquisition and resultant expressed transcript as an early event in the evolutionary history of a unique case of astroblastoma diagnosed in a 6 year old child with multiple recurrences after molecular analysis of 11 consecutive surgical resection samples [15]. Using the FoundationOne® platform, we discovered that our patient's astroblastoma harbored a truncation in *RBM10*, but there were no alterations in genes that are commonly altered in infiltrating gliomas (*IDH1, IDH2, ATRX, TP53*), low-grade gliomas (*BCOR, BCORL1, ERBB3, ATM*), or circumscribed glial neoplasms [1]. This platform did not include fusion information.

RBM10 encodes for RNA binding motif protein 10, a nuclear RNA binding protein involved in the regulation of alternative splicing. *RBM10* mutation is thought to be the disease-causing gene of TARP syndrome, a rare condition that causes several birth defects: Talipes equinovarus, Atrial septal defect, Robin sequence (micrognathia, glossoptosis and cleft palate), and persistence of the left superior vena cava. RNA binding motif (RBM) proteins are not necessarily a "family of proteins" designation, but refer to proteins having one or more RBM domains. *RBM10* is located on the X chromosome at p11.23. *RBM10* is alternatively spliced to produce RBM1-variant 1 and 2, which are most similar to *RBM5* in their amino acid structure [16]. *RBM5* was the first of RBM proteins that was shown to be a regulator of alternative splicing of apoptotic genes [17]. Given their structural similarity, *RBM10* was then assessed regarding its role in apoptosis. *RBM10* variants gene expression was shown to be significantly associated with the expression of proapoptotic Bax gene and the VEGF gene in breast cancer patient specimens [18]. Also, transient *RBM10* overexpression was correlated with significantly elevated TNF-alpha mRNA and protein levels and increased apoptosis in human breast adenocarcinoma cells [19]. In addition, *RBM10* is known as a tumor suppressor gene in lung cancer cells [20], and mutations in *RBM10* are thought to contribute to lung adenocarcinoma progression [21,22]. To date, there are no targeted therapies that directly address genomic alterations in *RBM10*.

Interestingly, our patient has two rare primary cancers, astroblastoma and mandibular ameloblastoma. Ameloblastoma is a locally invasive neoplasm of odontogenic origin that can involve the mandible or the maxilla. Ameloblastoma resembles normal enamel epithelium and ectomesenchyme histopathologically. Microscopically, ameloblastoma demonstrates uniform or mixed patterns of follicular, plexiform, acanthomatous, spindle, basal-cell like, desmoplastic and granular cells [23]. Interestingly, similar to astroblastoma, a high frequency of the BRAF-V600E mutation has been described in ameloblastoma; in particular, 70% of mandibular ameloblastomas have a *BRAF* mutation [24,25]. It is noteworthy to mention that even though near 40% of astroblastomas have been shown to have a BRAF-V600E mutation, our patient's astroblastoma did not carry this mutation. Detailed molecular analysis was not done on our patient's ameloblastoma. Ameloblastoma shows histologic and molecular similarities to basal cell carcinoma at the developmental stage, and patients with nevoid basal cell carcinoma syndrome [3] are prone to developing both basal cell carcinomas and odontogenic keratocysts, another neoplasm of the mandible and maxilla [3]. As such, mutation of the *PTCH1* gene, which is the responsible gene in Gorlin syndrome, was assessed in our patient's serum and was found to be negative. We do not know if our patient's ameloblastoma contains an *RBM10* mutation, but this may be the missing link between these two rare tumors in a young individual.

Conclusion

This case reaffirms prior literature pointing to heterogeneity of molecular aberrations in astroblastoma. *RBM10* gene abnormalities have been described in a number of solid cancers, and, along with *RBM5*, is thought to be one of the earliest and most frequent mutations in small cell lung cancer. However, *RBM10* gene aberration has not previously been described in glial neoplasms. This is the first report of *RBM10* truncation in astroblastoma. Interestingly, our patient has two rare primary tumors in the absence of clinical features of a particular syndrome. The genetic link between these two rare tumors in a young individual remains unclear.

Disclaimer

This article was prepared while Dr. Penas-Prado was employed at The University of Texas MD Anderson Cancer Center. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

Conflicts of interest

No conflict of interest, disclosures or sources of support to report.

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