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Case Report

Astrocytoma with high-grade features and MYBL1-MMP16 fusion

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ABSTRACT

Background: Gliomas represent the most common primary intraparenchymal brain tumors in adult and pediatric patients. Neuropathological work-up of these gliomas typically entails the determination of isocitrate dehydrogenase (IDH) mutational status, presence or absence of 1p/19q co-deletion, and O6 methylguanine-DNA methyl-transferase (MGMT) promoter methylation status.

Case Description: We present here an unusual case of a posterior fossa tumor in a 51-year-old female, which was initially diagnosed as astrocytoma with some high-grade features that recurred, displaying even more aggressive features such as infiltration and increased proliferative activity. Both the initially resected and recurrent tumor revealed MYBL1-MMP16 fusion, which is much more commonly found in pediatric low-grade gliomas and, to our knowledge has not been described in the context of an adult glioma.

Conclusion: The significance of MYBL1-MMP16 fusion in adult gliomas in relation to survival and likelihood of recurrence is, therefore, unknown and requires more extensive research.

Keywords: High-grade astrocytoma, Low-grade astrocytoma, MYBL1-MMP16 fusion

INTRODUCTION

Gliomas are the most common primary tumors of the central nervous system (CNS), with astrocytomas and oligodendrogliomas as the most common morphological subtypes.[4,9] Peak incidence for these neoplasms is said to be between the fifth and sixth decades of life, although oligodendrogliomas may also be found in young adults.[11] CNS gliomas typically present as mass lesions, with patients complaining of headache, nausea, and/or vomiting. Patients with oligodendrogliomas may also present with seizures. Much of the research on gliomas in recent years has focused on elucidating molecular signatures, which has led to the most recent 2021 World Health Organization classification of gliomas that combines histological with molecular findings to reach a final integrated diagnosis.[10] Another rationale behind investigations to elucidate molecular signatures is to find viable targets for therapeutic trials.[14]

The authors here report an unusual case of a posterior fossa tumor in a 51-year-old female who was initially diagnosed with astrocytoma with some high-grade features that recurred, displaying

even more aggressive features; this case is unusual in that both the initial and recurrent tumor revealed a MYBL1-MMP16 fusion, which, to our knowledge, has been previously described in the context of pediatric low-grade gliomas,[1] but not in adult gliomas.

CASE

Our patient is a 51-year-old female who initially presented with vertigo and, over two weeks, developed nausea, vomiting, headache, ataxia, and diplopia. On examination, she was found to have bilateral papilledema and mild right-sided dysdiadochokinesia. Initial investigations included computed tomography (CT) and magnetic resonance imaging (MRI) of the head, which revealed a cystic mass of the right cerebellar hemisphere measuring 4.1 × 3.2 × 3.2 cm [Figure 1]. The tumor exhibited a significant mass effect, causing compression of the 4th ventricle, resulting in obstructive hydrocephalus of the 3rd and lateral ventricles, as well as causing tonsillar herniation of 10 mm. A CT of the chest, abdomen, and pelvis showed no evidence of malignancy. The patient was admitted to the hospital and underwent insertion of an external ventricular drain followed by image-guided suboccipital craniotomy for gross-total resection of the cerebellar tumor.

Neuropathological examination of the resected tumor revealed a glial tumor comprised of Glial fibrillary acidic protein (GFAP)-positive astrocytic cells, some of which appeared to show fibrillary cytoplasmic processes. Rare examples of eosinophilic granular bodies and Rosenthal fibers were also found. Mitotic figures were scarce, and MIB-1/Ki67 was estimated at 5%. Vascular proliferations were also seen. In light of these findings, the tumor was histologically felt to be consistent with diffuse astrocytoma with high-grade features, as shown in Figure 2. Molecular analysis of the tumor did not reveal a BRAF V600E mutation or BRAF fusion but interestingly revealed MYBL1-MMP16 fusion. No mutations in IDH1/2, H3F3A, H3F3B, or TP53 were detected. TERT promoter mutation was not found, and ATRX immunohistochemistry showed retained expression in the tumor cells.

A postoperative MRI done four months after surgery showed a small infiltrative residual tumor behaving like a diffuse glioma [Figure 3]. One year later, the patient presented again with progressive ataxia. CT and MRI of the head completed at this time revealed a mass measuring 3.5 × 2.5 cm in the right cerebellar hemisphere. In addition, there was a 1.6 × 1.4 cm lesion in the right cerebellar peduncle with an enhancing cystic component in the 4th ventricle [Figure 4]. There was also associated herniation of the cerebellar tonsils and compression of the 4th ventricle with resultant hydrocephalus. The patient underwent emergent insertion of an external ventricular drain followed by redo suboccipital craniotomy for stealth-guided resection of both of these

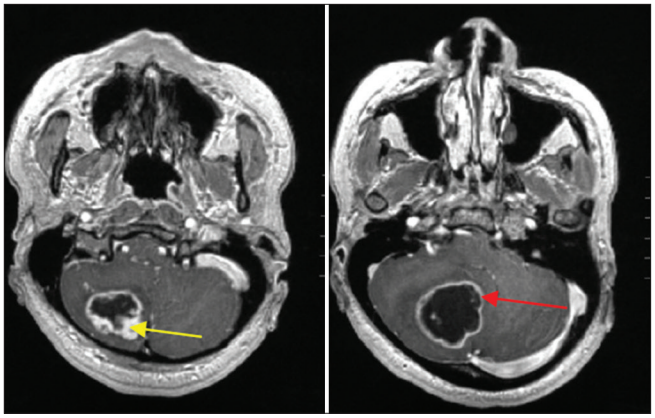

Figure 1: Preoperative magnetic resonance imaging (MRI). Axial MRI post gad showing the cystic lesion with enhancing mural nodule (yellow arrow), and enhancement of the cystic wall (red arrow).

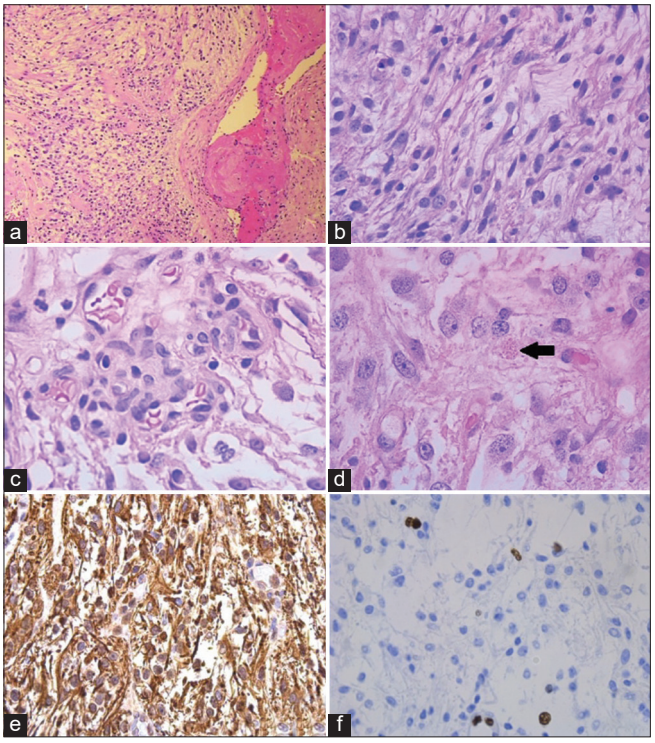

Figure 2: (a) Low magnification view of the tumor with a thrombosed blood vessel; (b) higher magnification showing glial cells with piloid processes; (c) example of microvascular proliferation; (d) example of eosinophilic granular body (arrow); (e) glial fibrillary acidic protein (GFAP) immunohistochemistry showing diffuse immunoreactivity; and (f) low Ki67/MIB-1 proliferative index.

lesions. Neuropathologic examination of the recurrent tumor also revealed an astrocytic tumor with morphological features similar to the original tumor. Unlike the initial tumor, the recurrent tumor also revealed focal evidence of infiltration and more frequent mitotic activity, with counts reaching 12/10 high-power fields. MIB-1/Ki67 proliferative index was also greater at 25% [Figure 5]. Molecular studies

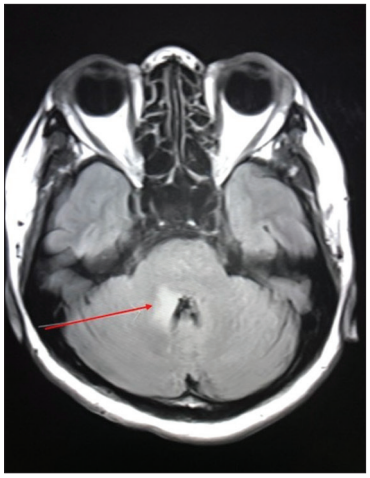

Figure 3: Postoperative magnetic resonance imaging four months after the first surgery showing a small infiltrative residual tumor (red arrow).

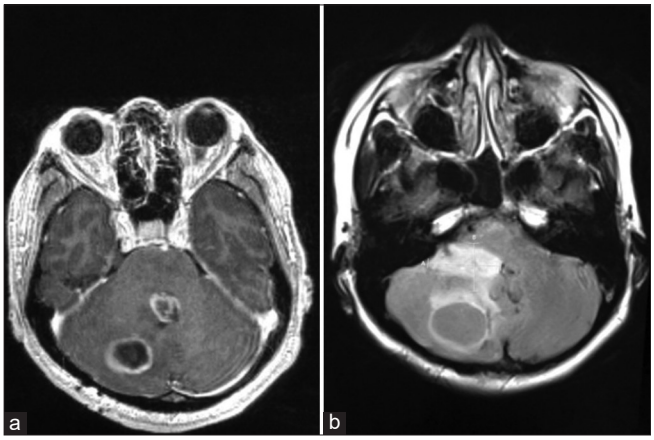

Figure 4: Eleven months after the first surgery, the patient presented with tumor recurrence. (a) Two lesions, one in the right cerebellar hemisphere, which is consistent with the location of the original tumor. Another lesion is seen centered in the fourth ventricle, likely arising from the residual tumor infiltrating the ventricular wall; (b) axial flair magnetic resonance imaging shows a portion of the tumor arising from the right lateral aspect of the fourth ventricular wall.

were performed on the recurrent tumor and revealed the same MYBL1-MMP16 fusion as in the initial tumor. The patient was referred to the neuro-oncology service for adjuvant therapy.

Unfortunately, methylation profiling was not available at the time of reporting. The patient traveled out of the country and was lost in follow-up.

DISCUSSION

We present here an unusual case of a posterior fossa tumor in a 51-year-old female, which was initially diagnosed as

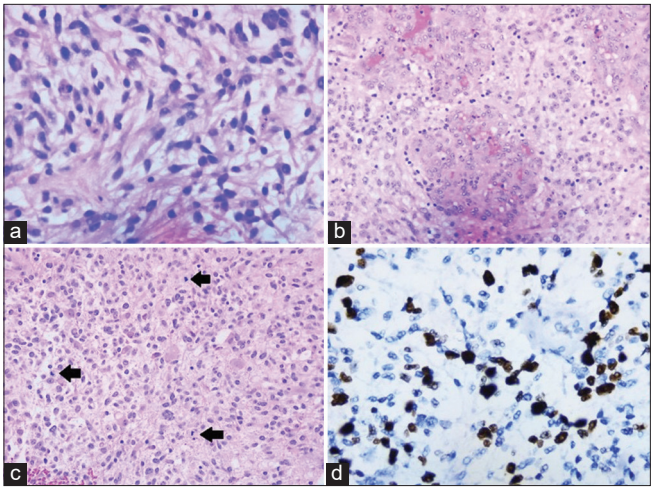

Figure 5: Neuropathological findings from the second tumor (a) piloid cells with fibrillary cytoplasm; (b) microvascular proliferation; (c) mitotic activity (arrows); and (d) Ki67/MIB-1 proliferative index estimated to reach 25%.

astrocytoma with some high-grade features that recurred, displaying even more aggressive features. What is unusual about our patient is that although the recurrent tumor revealed aggressive features (infiltration, frequent mitotic activity, and elevated proliferative index), molecular analysis still revealed a MYBL1-MMP16 fusion, which is more in keeping with an indolent glioma and no additional mutations on top of those found in the initial tumor were detected. The majority of those gliomas seem to occur in pediatric patients and young adults, while presentations in older adults (>50 years) are much less common.[3] Given the paucity of those gliomas in adults, especially those arising in the posterior fossa, there is little evidence regarding the clinical and biological features of these tumors in this population. Moreover, the reasons behind increased recurrence and poorer prognosis in adults remain largely unknown.[7] MYBL1-MMP16 fusion is known to be associated with diffuse pediatric low-grade glioma.[20] MMP16 has been demonstrated to enhance glioma cell migration *in vitro,* and metalloproteinase matrix protein mutations have been implicated in brain infiltration of glioma cells.[18,21] This could explain the fact that despite gross total resection of the tumor, postoperative MRI showed a residual diffuse infiltrative lesion [Figure 4].[8]

Early-described mutations in astrocytomas, such as PAs, include mutations to PDGF ligands and PDGF receptors, as well as inactivating mutations to TP53.[2] Additional known mutations include BRAF V600E mutations and B-K fusions, which lead to aberrant ERK/MAP kinase pathway activation; however, these were primarily described in pediatric patients.[6] Theeler *et al*. later discovered that the BRAF V600E mutation was rare in adult populations, while B-K fusions were identified in 20% of adults. RAS and PIK3CA

mutations may also be implicated in low-grade gliomas in adults.[17] MYB or MYBL1 alterations are quite uncommon in CNS gliomas. They have been reported in the context of diffuse astrocytoma and angiocentric glioma, but studies of this gene in CNS tumors are limited.[5] Qaddoumi *et al*. (2016) studied molecular alterations in 91 low-grade neuroepithelial tumors (dysembryoplastic neuroepithelial tumor (DNET) = 22, oligodendroglioma = 20, diffuse astrocytoma = 17, ganglioglioma = 17, and angiocentric glioma = 15) using parallel sequencing and various targeted molecular genetic methods.[12] The authors observed MYBL1 fusions in 14 angiocentric gliomas and MYB fusion in a single case of oligodendroglioma and MYB or MYBL1 rearrangements in seven diffuse astrocytomas.[13,15] To the best of our knowledge, our case is the first of an adult astrocytoma with morphological features of an astrocytoma with high-grade features (neoplastic cells with fibrillary cytoplasmic processes, eosinophilic granular bodies, Rosenthal fibers, and vascular proliferations) to reveal MYBL1-MMP16 fusion. At the same time, MYBL1 fusions have more commonly been reported in the context of pediatric low-grade gliomas.[16,17,19], the significance of such fusions in adult gliomas is still yet to be determined, given the scarcity of these cases.

CONCLUSION

Herein, the authors present an unusual case of a recurrent astrocytic tumor with histopathological features compatible with an astrocytoma with high-grade features. The MYBL-MMP16 fusion found in both the initial and recurrent tumor has been reported in pediatric low-grade gliomas, but its significance in adult gliomas is unclear and requires further investigation. Larger scale research is necessary to determine their clinical significance and potential prognostic and therapeutic implications. Cases such as ours also reiterate the notion that neuropathologic diagnosis of CNS tumors must be a true integration of histopathological features and molecular data rather than the misconception that diagnostic and management decisions can be made solely based on molecular data. Further, an understanding of molecular features may provide insight into the more aggressive nature of these tumors in this population.

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Ethical approval

Institutional review board approval is not required.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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