Antitumor Effect of Selumetinib for Brainstem Glioma in an Adult With NF1: A Case Report

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BACKGROUND AND IMPORTANCE: NF1 is a known tumor predisposition syndrome associated with various tumors of the nervous system, including low-grade glioma in the pediatric population. NF1-associated brainstem tumors are less clinically progressive and rarely result in early death. However, a small subset of brainstem gliomas may act more aggressively in adults, especially when contrast enhancement appears. However, standard therapy for NF1-associated brainstem glioma remains controversial, and there is limited information available on the pathological and genetic findings.

CLINICAL PRESENTATION: A 38-year-old man presented with diplopia and was diagnosed with a midbrain tumor on MRI. The tumor increased in size during a 2-month follow-up period, and the patient underwent an open biopsy by the occipital transtentorial approach. Histopathological diagnosis revealed a low-grade glioma, isocitrate dehydrogenase wild type, and H3 wild type. An *NF1* mutation was detected using a cancer gene panel test. The MAPK kinase inhibitor, selumetinib, was prescribed as first-line treatment. The patient achieved a good clinical response, with impressive radiological regression of the disease and no major adverse events. After 6 months of selumetinib use, the patient discontinued the medication. However, the disease recurred 6 months later, prompting the initiation of carboplatin therapy.

DISCUSSION AND CONCLUSION: Primary treatment with MAPK kinase inhibitors can lead to tumor regression in brainstem glioma in an adult patient with NF1. We recommend that patients with brainstem glioma undergo biopsy and mutation testing, especially those with an unusually aggressive clinical course.

KEY WORDS: Gliomas, NF1, Brainstem, MEK inhibitor

NF1 is a neurocutaneous disease inherited in an autosomal dominant manner, with the prevalence estimated to be between 1 in 2000 and 1 in 5000.[1-3] NF1 is a genetic predisposition disorder caused by loss-of-function alterations in the *NF1* gene, a negative regulator of the MAPK pathway. Approximately 15%-20% of patients with NF1 will develop low-grade gliomas (LGGs).[4,5]

NF1-associated brainstem tumors are less clinically progressive and rarely result in early death, especially when compared with sporadic brainstem gliomas such as diffuse intrinsic pontine glioma.[6,7] However, a small subset of brainstem gliomas may act more aggressively in adults, especially when contrast enhancement appears.[8,9] Because NF1-associated gliomas often follow a slow clinical course and do not require immediate treatment, surgical sampling and molecular studies have historically been limited. Nevertheless, recent observations indicate that pilocytic astrocytomas, particularly in adults, can undergo anaplastic transformation, which correlates with more aggressive tumor behavior.[9] Unfortunately, there is no standard therapy for these gliomas, and limited information is available on the pathological and genetic findings.

MAPK kinase (MEK) inhibitors are used for the treatment of NF1-associated tumors and, in combination with *BRAF* inhibitors, for *BRAF*-mutant cancers. Selumetinib (ARRY-142886, AZD6244) is an orally available, selective MEK 1/2 inhibitor

ABBREVIATIONS: LGG, low-grade glioma; **MEK,** MAPK kinase.

approved for children with NF1 and symptomatic, inoperable plexiform neurofibromas in Japan.[10] A phase II trial evaluating the efficacy and safety of selumetinib monotherapy in pediatric patients with treatment-refractory recurrent LGG has demonstrated favorable antitumor effects in patients with *BRAF* mutations and *NF1*.[11] However, its efficacy in adult patients with NF1-associated brainstem gliomas has not been well-documented.

In this study, we present a case of aggressive brainstem glioma in a 38-year-old man with NF1 who demonstrated clinical and radiological improvement with treatment using selumetinib. This case highlights the potential of selumetinib as a treatment option for adult patients with NF1-associated brainstem gliomas, a population for which there are currently limited data.

CLINICAL PRESENTATION

A 38-year-old man presenting with diplopia was referred to our institution. The patient developed double vision 3 months ago. The patient presented with a family history of NF1 and displayed café au lait spots along with iris Lisch nodules, fulfilling the diagnostic criteria for NF1. MRI showed a well-demarcated intra-axial tumor in the dorsal part of the midbrain, displaying hyperintensity on fluid-attenuated inversion recovery imaging and a small gadolinium enhancement (Figure 1A). Because the tumor was growing with an increase in the enhancement lesion during a follow-up period of 2 months (Figure 1B), the patient underwent an open tumor biopsy by the occipital transtentorial approach. The postoperative course was uneventful. Histopathological examination revealed spindle-shaped tumor cells exhibiting multipolar or bipolar delicate eosinophilic processes. There was noticeable pleomorphism in both cell and nuclear size. No mitotic figures or necrosis were observed. Thin-walled dilated blood vessels were relatively common. Immunohistochemically, the tumor cells were diffusely positive for GFAP and Olig2, showed a Ki-67 labeling index of 1%-5%, and were negative for IDH1 R132H (Figure 2). As a result of genetic analysis, *IDH1*, *IDH2*, *H3F3A* (*H3-3A*), *HIST1H3B*, *HIST1H3C*, and the *TERT* promoter were all found to be wild-type. An integrated diagnosis revealed a LGG, isocitrate dehydrogenase wild type, and H3 wild type. The patient was followed for 3 months without treatment but experienced worsening of headache and diplopia, and MRI showed enlargement of the tumor with increasing enhancement (Figure 1C). The following gene mutations were detected in the cancer gene panel test (Foundation One): *NF1*, *ATRX*, *IRF2*, *KMT2D* (*MLL2*), *MST1R*, *MTAP*, *CDKN2A/B* loss, and *TEK*. No fusion gene mutations were observed as biomarkers other than gene mutations. An expert panel, a molecular tumor board composed of multidisciplinary specialists, recommended the use of the MEK 1/2 inhibitor, selumetinib. In patients with NF1,

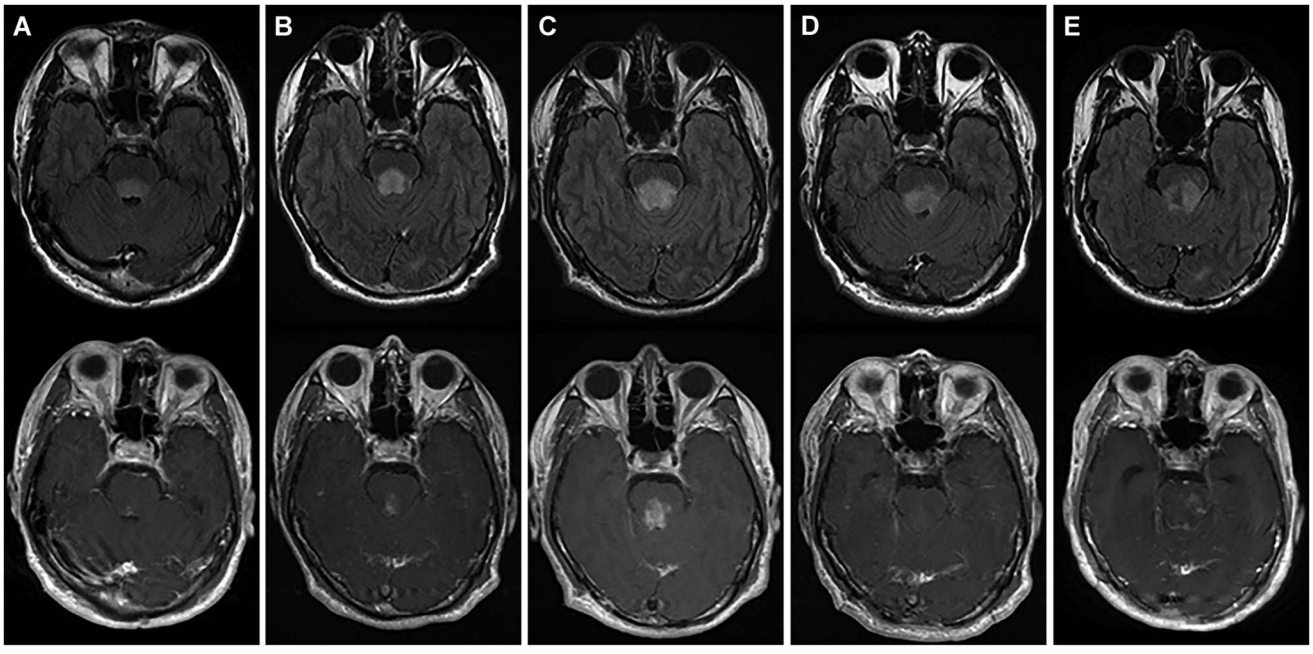

FIGURE 1. *Sequential MRI. The upper images are FLAIR, and the lower images are GdT1.* **A**, *An intra-axial tumor is identified in the dorsal part of the midbrain on FLAIR imaging. The tumor shows a small enhancement on gadolinium-enhanced T1-weighted imaging.* **B**, *During the follow-up period of 2 months, the tumor enlarges and shows increasing enhancement.* **C**, *At 3 months postoperatively, the tumor enlarges and shows increasing enhancement.* **D**, *After 2 months of selumetinib use, the tumor shrinks and shows the disappearance of enhancement.* **E**, *Six months after discontinuing selumetinib, the tumor exhibited re-enlargement accompanied by increased enhancement. FLAIR, fluid-attenuated inversion recovery.*

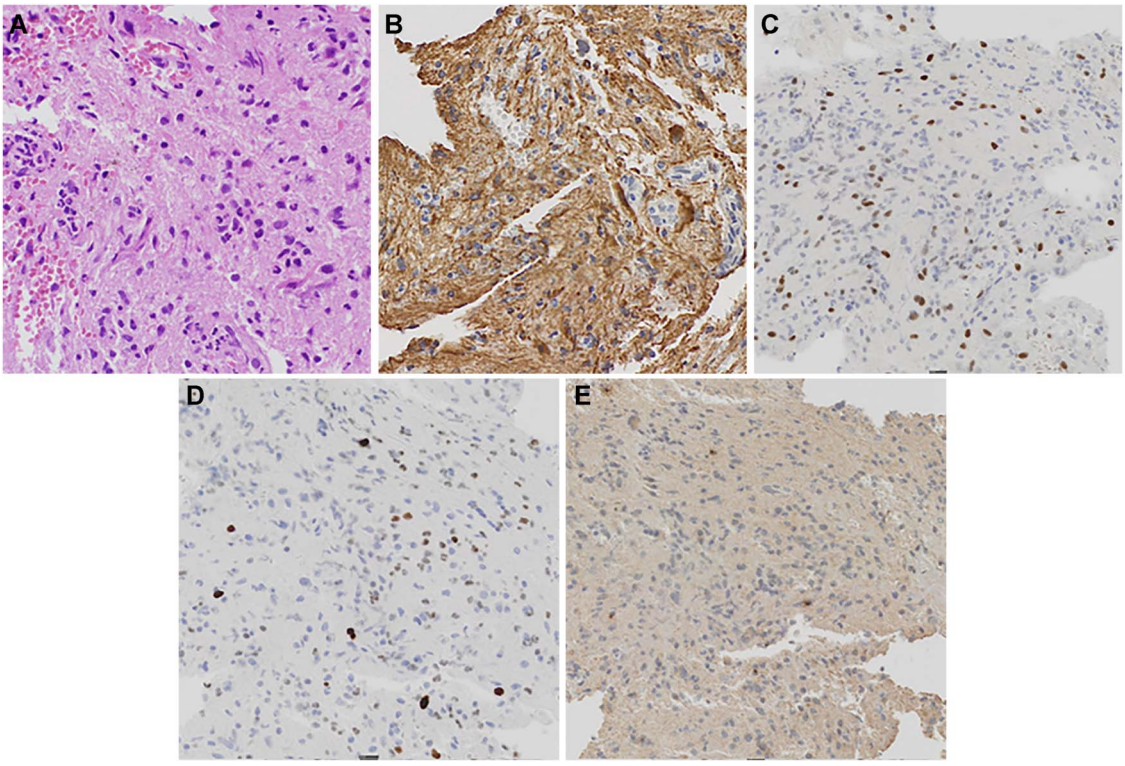

FIGURE 2. *Microscopic appearance and immunohistochemistry.* **A**, *A moderately cellular tumor is observed. It is composed of spindle-shaped cells that extend multipolar or bipolar delicate eosinophilic processes, and these cells and nuclei are unequal in size. There are no mitoses or necrosis. Thin-walled dilated vessels are relatively common.* **B**, *Tumor cells display diffusely positive staining for GFAP.* **C**, *Tumor cells display diffusely positive staining for Olig2.* **D**, *Only a few tumor cells are positive for Ki-67.* **E**, *Tumor cells are negative for IDH1 R132H.* **A-E**, *Original magnification ×200.*

NF1 mutations cause RAS-mediated overactivation of the MAPK pathway, which selumetinib effectively suppresses by selectively inhibiting MEK 1/2. After approval by the hospital ethics review committee and informed consent, the patient received selumetinib 25 mg/m^2 orally twice a day (off-label use). Two months after administration, the clinical symptoms of headache improved, and MRI showed shrinkage of the tumor with disappearance of enhancement (Figure 1D). The patient experienced only dry skin without major adverse events and was able to continue the treatment. The cutaneous neurofibroma did not shrink. The patient's symptoms improved, and MRI showed a tendency toward reduction in the contrast-enhancing lesion; therefore, selumetinib treatment was discontinued after 6 months by mutual agreement with the attending physicians. Unfortunately, 6 months after the cessation of selumetinib, the patient experienced worsening of diplopia and gait disturbance, and MRI showed re-enlargement of the tumor with increasing enhancement (Figure 1E), indicating a recurrence that necessitated further medical intervention. Because of the patient's financial constraints, selumetinib could not be used, and the patient is currently being treated with carboplatin.

DISCUSSION

Although earlier guidelines recommended avoiding biopsy in presumed NF1-related LGGs, recent perspectives emphasize the necessity of molecular profiling as part of diagnostic and management strategies.[12,13] Genome-wide studies have demonstrated unexpectedly intricate molecular alterations in gliomas from patients with NF1, particularly in younger individuals.[14] Through next-generation sequencing, copy number analysis, and DNA methylation profiling of gliomas from 47 patients with NF1, the tumors were molecularly classified into 2 distinct groups: a low-grade group harboring only NF1 inactivation and a high-grade group with additional oncogenic alterations such as *CDKN2A/B* homozygous deletion and *ATRX* mutation. The low-grade group predominantly occurred in childhood, followed a more indolent clinical course, and responded well to MEK inhibitor monotherapy. By contrast, the high-grade group primarily arose during adulthood, exhibited considerable epigenetic heterogeneity, showed a more aggressive clinical behavior, and often demonstrated limited response to MEK inhibitors alone.[15] In the present case, the presence of *ATRX* mutation and homozygous

deletion of *CDKN2A/B* supported an aggressive nature and required biopsy and therapeutic intervention.

Molecularly targeted therapy, especially treatment with MEK inhibitors, has emerged as a highly effective therapeutic option for pediatric NF1-associated LGGs requiring intervention. Although data on efficacy and toxicity in adult patients remain limited, a recent study involving 9 cases of NF1-associated gliomas demonstrated generally good tolerability of MEK inhibitors. No severe adverse events were reported, and toxicities were limited to known effects such as skin rash, indicating an acceptable safety profile even in molecularly defined tumors in adult patients.[11,16,17] Although skin rash is commonly seen in patients treated with selumetinib, as previously reported, the patient in this report experienced only slight skin irritation and was able to continue the treatment for 6 months without the need for dose reduction. The patient completed treatment with selumetinib after 6 months by agreement between the attending physicians and the patient. However, it is important to note that the tumor recurred 6 months after the cessation of selumetinib treatment. This raises questions about the long-term efficacy of selumetinib and whether it might contribute to tumor malignancy. Consequently, additional clinical experience is essential to assess the durability and safety of MEK inhibition over time. Emerging insights into NF1-associated LGGs have reshaped both diagnostic and therapeutic paradigms and raised numerous questions that demand systematic investigation for optimal care.[4] The natural progression of NF1-associated LGG indicates a tendency toward eventual senescence, thus necessitating a thorough examination of the natural history after MEK inhibitor treatment.[18]

CONCLUSION

Selumetinib has potential effectiveness against NF1-related adult brainstem gliomas. As distinct genetic abnormalities in the MAPK cascade have been increasingly implicated in LGG, molecularly guided diagnostics through biopsy have become a critical component in the evaluation process. There are many issues regarding its proper duration of use and evaluation, and more molecular information and case studies are needed.

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