Significant response to targeted therapy for Cervico-Medullary pediatric low grade glial tumors with BRAF^{V600E} mutation

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Abstract

Purpose: Children with unresectable cervico-medullary low-grade glial tumors (CMTs) have poor progression-free survival when treated with conventional chemotherapy and radiation. The BRAFV600E mutation occurs in many low-grade glial tumors that are amenable for targeted therapy using mutation-specific kinase inhibitors. However, these inhibitors' effectiveness and best treatment duration in these tumors setting are not defined. Method: Retrospective description of three cases of childhood cervico-medullary low-grade tumor with BRAFV600E mutation and their response to BRAF inhibitor therapy with Dabrafenib. Results: Dabrafenib therapy was provided as first line for two patients and second line for one patient with CMTs. All patients experienced rapid tumor regression and significant and durable clinical and radiological improvement. The targeted therapy was tolerated well in two patients despite the long-term use of 3-5 years, while one patient stopped therapy after 1 year due to serious adverse event that was reversible upon discontinuing therapy. Conclusion: Dabrafenib was effective and well-tolerated in two of the three patients. We observed clinical and radiological response that demonstrates the role of targeted therapy as alternative for adjuvant chemotherapy and radiation in BRAFV600E unresectable tumors. These cases indicate the need to re-evaluate the therapeutic approach in children with CMT, the early use of Dabrafenib and the treatment duration and to explore the possible adverse and late effects of this promising therapy.

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Abstract

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mutation occurs in many low-grade glial tumors that are amenable for targeted therapy using mutation-specific kinase inhibitors. However, these inhibitors' effectiveness and best treatment duration in these tumors setting are not defined.

Method : Retrospective description of three cases of childhood cervico-medullary low-grade tumor with $BRAF^{V600E}$mutation and their response to BRAF inhibitor therapy with Dabrafenib.

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Conclusion : Dabrafenib was effective and well-tolerated in two of the three patients. We observed clinical and radiological response that demonstrates the role of targeted therapy as alternative for adjuvant chemotherapy and radiation in $BRAF^{V600E}$unresectable tumors. These cases indicate the need to re-evaluate the therapeutic approach in children with CMTs, the early use of Dabrafenib and the treatment duration and to explore the possible adverse and late effects of this promising therapy.

Keywords: Pediatric Low-grade Glioma, Cervico-medullary tumor, Central nervous system, Dabrafenib, $BRAF^{V600E}$

Abbrevistion	Definitions
CMTs	cervico-medullary tumors
pLGG	pLGG
MAPK	mitogen-activated protein kinase
CNS	central nervous system
OS	overall survival
PFS	progression free survival
CTCAE	common terminology criteria for adverse events
IRB	institutional review board
MRI	magnetic resonance imaging
RAPNO	response assessment in neuro-oncology criteria
CPAP	continuous positive airway pressure
BPAP	bilevel positive airway pressure
WHO	world health organization
AHI	apnea hypopnea index
BRAFi	BRAF inhibitor
SAE	severe adverse event
MR	minimal response
PR	partial response
CR	complete response

Abbreviations: CMTs, cervico-medullary tumors; pLGG,pediatric low-grade glioma; MAPK,mitogen-activated protein kinase; CNS,central nervous system; OS,overall survival; PFS,progression free survival; CTCAE,common terminology criteria for adverse events; IRB,institutional review board; MRI,magnetic resonance imaging; RAPNO,response assessment in neuro-oncology criteria; CPAP,continuous positive airway pressure; BPAP,bilevel positive airway pressure; WHO, world health organization; AHI, apnea hypopnea index; BRAFi, BRAF inhibitor; SAE,severe adverse event; MR, minimal response; PR, partial response; CR, complete response.

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Introduction

Pediatric low-grade glioma (pLGG) is the single most common form of primary central nervous system tumor, accounting for over 30% of CNS tumors in this age group. The standard of care for patients with unresectable or progressive pLGG consists of chemotherapy with radiotherapy in progressive cases.[1] Current chemotherapy strategies achieve tumor control in 40% to 50% of patients.[2,3] Radiotherapy achieves excellent tumor control, approaching 80%, but is accompanied by an increased risk of secondary malignancies, vasculopathy, and cognitive adverse effects.[4,5]

Activation of the MAPK signaling pathway represents a hallmark of pediatric low-grade gliomas. The most frequently mutated gene within MAPK pathway is BRAF. BRAF is an essential mediator and the $BRAF^{V600E}$ most frequent point mutation leads to constitutive kinase activation. It is highly prevalent in melanoma and has also been described in other cancers, including papillary thyroid cancer and colon carcinoma. It is the most common somatic mutation in low-grade gliomas, found in 15% of pLGG, and is associated with a worse response to conventional chemo-radiation treatments.[6]$BRAF^{V600E}$ is common in pleomorphic xanthoastrocytomas (40-80%), diffuse Astrocytoma (30-40%), and ganglioglioma (25-45%), while it is less common in pilocytic astrocytoma (5-10%) or glioneuronal tumors (5%). Supratentorial lesions are also more likely to harbor BRAF mutation compared to cerebellar lesions. However, $BRAF^{V600E}$ mutation can be found in any location in the CNS, 33% of which are located in the midline (diencephalon and brainstem).[7] Tumors in these locations are often not biopsied, and medical therapy (radiation and chemotherapy) is initiated blindly under the assumption that all pLGG will have a favorable outcome. However, pLGG with $BRAF^{V600E}$ have worse OS and PFS compared to other pLGG with conventional therapies. In the SickKids cohort, $BRAF^{V600E}$ tumors continued to progress without reaching a plateau. Five-year PFS for $BRAF^{V600E}$ and wild-type BRAF pLGG was 50.1% and 72.8%, respectively, 10-year PFS was 27% and 60.2% respectively, and 10-year OS was 83.9% and 92.1%, respectively.[8] Thus providing an effective medical therapy to pLGG with $BRAF^{V600E}$ mutation is an unmet medical need. We describe three cases of unresectable CMTs with BRAF mutation successfully treated by BRAF inhibitors for maintaining local control of tumor progression while also providing further relief of symptoms as an alternative to aggressive resection or radiation.[9]

Methods

Three patients with unresectable CMTs harboring BRAF mutation identified with NGS assay for 22 genes using the "Colon and Lung Cancer Panel" (Ampliseq).[10] After informed consent was provided, $BRAF^{V600E}$ mutated CMTs were treated with BRAF inhibitor approved by the local IRB. Dabrafenib was provided in managed access program by Novartis at a daily dose divided bid of 5.25 mg/kg/day up to 12 years of age or 4.5 mg/kg/day above 12 years. Interdisciplinary periodic follow up included neuro-oncology, neuro-ophthalmology, cardiology, dermatology, endocrinology, and blood and urine tests. Response evaluation included clinical outcome measures and radiological response assessment for low-grade gliomas according to the reduction in tumor size, as measured by MRI according to the modified RAPNO for pLGG.[11,12,13] Grading of toxicities is based on CTCAE v4.

Case series

Case 1

A 13-year-old girl presented with a several-year history of mild obstructive sleep apnea, treated with tonsillectomy, a year history of mild hoarseness and new onset of instability during dance lesions. Clinical findings included partial left vocal cord paralysis on endoscopic laryngoscopy, left horizontal nystagmus, abnormal tandem gate tend to fall to the left, and left-hand tremor. On MRI, a Cervico-Medullary tumor with exophytic component involving brainstem down to foramen magnum. Sleep apnea test diagnosed mild

obstructive sleep apnea. The patient received empiric first-line chemotherapy of weekly Vinblastine for 12 months with stable MRI. However, due to clinical progression, including moderate central and obstructive sleep apnea (AHI-7) and pCO2 retention, therapy with nocturnal CPAP started followed by BPAP therapy. Open biopsy performed with a diagnosis of low-grade glioma WHO grade I with $BRAF^{v600e}$ mutation, negative for BRAF fusion, IDH-1, and H3K27M mutation, P53 was positive in numerous cells with wild-type germline P53. To avoid long-term effects of radiation, oral Dabrafenib started with a partial response on MRI after four months (Fig. 1), and clinical response, including decreased nystagmus, improved tandem gate, and decreased sleep apnea (AHI-4) with weaning from BPAP therapy. The patient reported minor dermatologic grade 1 AE of curly hair and continues therapy after five years with stable disease on MRI and sustained clinical response.

Case 2

A 5-year-old boy presented with several weeks of slurred speech, tongue deviation and right shoulder weakness. MRI demonstrated a Cervico-Medullary tumor involving pons, medulla and extending down to the level of C3-4. Partial resection was performed, with diagnosis of ganglioglioma WHO grade I. Post-operative neurological sequel included right hemiparesis that required rehabilitation. After five years of stable disease, at 10-years of age, progression was demonstrated on MRI followed by increased right hemiparesis and right vocal cord paralysis on endoscopic laryngoscopy, with normal gag reflex and normal sleep test. We recommended BRAF analysis, and the tumor was positive for $BRAF^{v600e}$ mutation and negative for BRAF fusion, CDK2A deletion, and H3K27M mutation. Upfront BRAFi therapy was started and after four months on oral Dabrafenib therapy, remarkable clinical response was observed including decreased hemiparesis as well as marked decrease in tumor size on MRI (Fig. 2). The patient gradually resumed full sport activities and continues BRAFi after three years on therapy without any significant AEs.

Case 3

7-year-old boy presented with several years history of nasal speech and two months of ataxia, left hemiparesis, and facial weakness. MRI diagnosed a mildly enhancing cervico-medullary tumor involving the medulla down to the level of C2. Left vocal cord paralysis demonstrated on endoscopic laryngoscopy with mild aspiration of fluids. On Sleep test moderate central sleep apnea (AHI-22.1) including pCO2 retention was diagnosed, and started nocturnal BPAP therapy. Radiation therapy was considered. A biopsy confirmed the diagnosis of Ganglioglioma WHO grade I with $BRAF^{v600e}$ mutation, negative for CDK2A deletion and H3.3K27M mutation. First-line therapy with Dabrafenib was started, and after a month of therapy gradual clinical response including improved speech, decreased sleep apnea (AHI-2) on BPAP therapy and decreased left hand weakness as well as mild decrease of tumor size was noticed on MRI (Fig. 3). Therapy was temporarily withheld due to fever and pneumonitis (AE grade 2) with enlarged mediastinal lymph nodes (SAE Grade 3) treated with steroids. The lymph nodes were biopsied with diagnosis of reactive lymphadenitis suggesting sarcoid-like reaction.[14] Treatment was reintroduced after resolving clinical and radiological findings. Following several months on therapy, the patient continued having clinical benefit on therapy, yet due to recurrence of fever and mediastinal lymphadenopathy on chest CT scan the local IRB ruled for termination of therapy due to recurrent SAE. Due to minor clinical progression, monthly Carboplatin was started with stable clinical and radiological response.

Discussion

This case series of BRAF ^{V600E} mutated CMTs represents a unique example of the importance of early molecular diagnosis and the role of BRAFi as first-line therapy for selected cases of pLGG, especially in young children. The first case was treated by Vinblastine with temporary response and switched to BRAFi following a biopsy that confirmed diagnosis of LGG with BRAF mutation. The second case was treated by a partial resection with a neurological sequel and after progression to a size that required urgent radiation, BRAF analysis was performed, and a mutation was found. BRAFi therapy led to a substantial clinical response and regression of the tumor. The third case was biopsied right at his stormy presentation with sleep apnea and aspirations that also raised the question of urgent radiation. As BRAF mutation was found,

BRAFi therapy was started with clinical improvement.

CMTs are rare intramedullary tumors diagnosed as slow-growing mainly low-grade gliomas and ganglioglioma that typically present with a long duration of symptoms. Patients whose tumor epicenter is within the medulla first develop nausea and vomiting, obstructive hydrocephalus, failure to thrive, lower cranial nerve dysfunction, chronic aspiration, sleep apnea, and head tilt. When the tumor epicenter is in the upper cervical spine, characteristic features are neck pain, hyper- or hyporeflexia, progressive weakness with changes in gait and motor regression in younger patients,.[9] in series of CMTs, diagnosis of low-grade tumors was made in 84% of patients. Despite that subtotal resection was performed in 45% and biopsy only in 39%, most of the patients required adjuvant therapy including chemotherapy in 87% and 67% received radiotherapy.[9] Recurrent tumor developed in 45% of the patients, and reported 5- and 10-year treatment-free survival estimates are 64.7% and 45.3%, respectively. The location of cervico-medullary tumors and the clinical manifestations raises therapeutic dilemma, as resection is feasible only in selected cases[1] and chemotherapy regimens for this specific group of pLGG usually result in a high rate of progression that may require radiation. The advances in molecular stratification of pLGG and clinical trials implementing BRAF and MEK-inhibitors[18]provided the basis for introducing BRAF inhibitors for CMTs as effective first line therapy for these complicated tumors.

As a group, pLGG with $BRAF^{V600E}$ mutation have worse OS and PFS compared to other pLGG with wild-type BRAF.[19]This mutation, especially in combination with CDKN2A deletion, is associated with increased risk for transformation into HGG; an event that may occur 10-20 years after the initial diagnosis.[20] Kieran et al[21] reported the phase II results of Dabrafenib in pediatric patients with $BRAF^{V600E}$ mutated relapsed or refractory low-grade glioma with an overall response rate of 44% and one year PFS of 85%. The treatment was well tolerated with grade 3/4 treatment-related AEs in 28% of the patients. Tabori et al reported encouraging response to BRAF inhibition in a BRAF mutated pLGG cohort, with OR of 80% (MR 27%, PR 50% and CR 3%).[22]

The caveats of the targeted therapy include possible BRAF/MEK inhibitor therapy adverse effects based on adult melanoma patients[24] with preliminary side effects profile in pediatric patients.[20,23,25] Interdisciplinary follow up and monitoring for adverse events are required as long term side effects in children are unknown. In addition, limited data is available regarding the appropriate therapy duration and timing for discontinuation of BRAFi therapy. Aguilera et al. reported a patient with refractory brainstem ganglioglioma treated with Vemurafenib, which had successfully been retreated with the same drug after recurrence post-discontinuation.[26] Tabori et al reported 76.5% of the $BRAF^{V600E}$ tumors had rapid regrowth after BRAF inhibition stopped, however reintroduction of BRAF inhibition alone or combined with MEK inhibition resulted in 90% response rate of the progressed tumors.[22] Another challenge is intrinsic and acquired resistance mechanisms to BRAF inhibition with the recovery of MAPK signaling. Nicolaides et al described the role of combined BRAF-MEK inhibition to possibly prevent and overcome this resistance .[27]

Confronting CMTs as a unique subgroup of pLGG in children raises several questions: First, the role for debulking surgery which is sometimes very difficult, can never achieve complete removal and is frequently accompanied by neurological damage. The role of such operation in the face of the efficacy of BRAFi is questionable.

The role of conventional chemotherapy with Vinblastine or Vincristine Carboplatin is also questionable, having in mind the relative limited long-term efficacy of these therapies, especially when the tumors harbor BRAF mutation.

We, therefore, suggest, when confronted with CMTs to perform early biopsy and molecular diagnosis and to treat $BRAF^{V600E}$mutated CMTs with BRAFi inhibitor as first-line therapy, thereby avoiding a possibly futile operation, unnecessary neurological damage, and achieving a better outcome.

Conclusions

These case series highlight the potential role of upfront BRAF inihibitor for the subset of pLGG that harbor

$BRAF^{v600e}$ mutation deemed unresectable. The rapidly achieved clinical and radiological response using targeted therapy for CMTs provides a venue to avoid debulcking surgery and delay or even avoid radiation therapy. It can improve progression-free survival and overall survival as currently explored in randomized clinical trials. The unique location of CMTs harbors the high risk of this tumor as manifested clinically with abnormal sleep patterns, evolving neurological deficit, and risk for aspiration. This unique clinical presentation with the high risk of progression portrays the role of BRAFi as an example for first line therapy for selected patients. Notwithstanding the promising role of BRAFi in pLGGs with $BRAF^{v600e}$, this therapy mandates careful interdisciplinary follow-up to evaluate potential side effects and randomized clinical trials exploring this promising targeted therapy.

Compliance with ethical standards

Conflict of interest: the authors declare that they have no conflict of interest.

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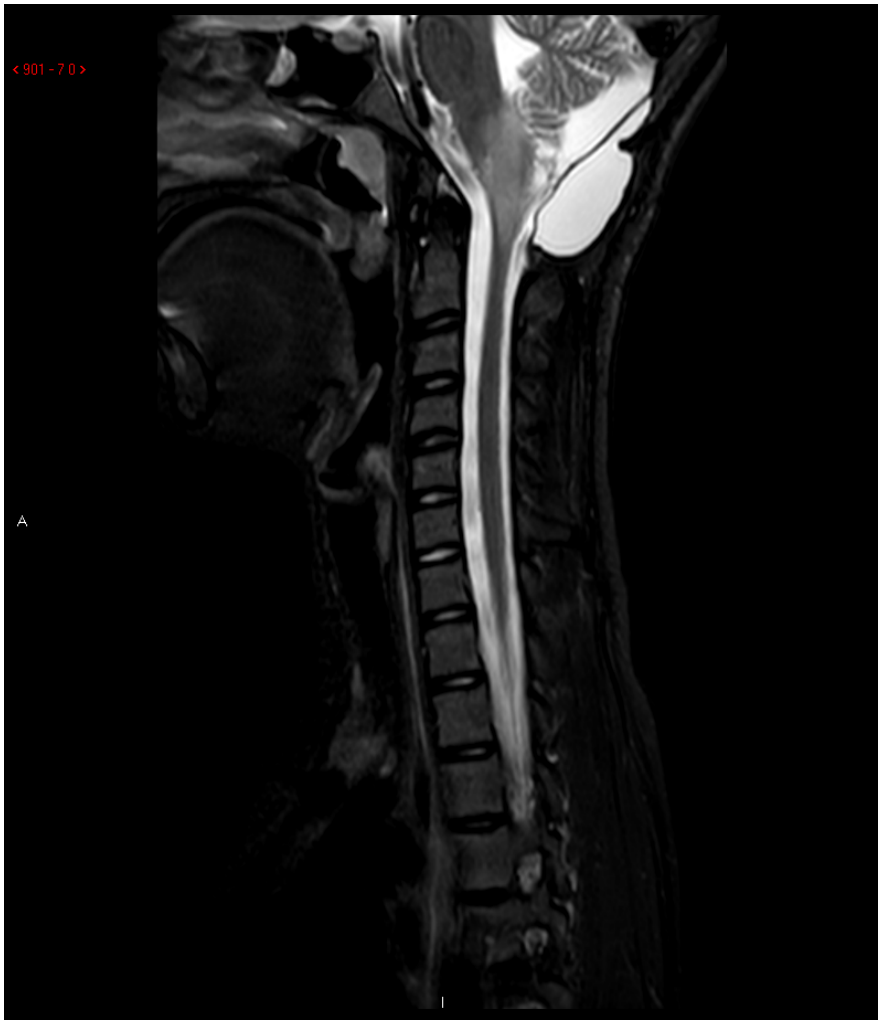

Figure 1: Images of upper cervical spine taken pretreatment (Upper row: A, B) and five months following treatment (Lower row: C, D) including sagittal fat-suppressed T2 (A, C) and post-contrast T1 images (B, D). An expansile infiltrative lesion is noted within the cervico-medullary junction involving area postrema (asterisk on A). The lesion shows patchy enhancement on post-contrast T1 images (arrows on B). Following treatment, there is no significant change in the size or extension of the tumor (compare A and C). However, post-contrast enhancement has decreased significantly. Note sub-occipital craniotomy done for decompression at the level of the foramen magnum with small residual pseudo-meningocele (arrow on C).

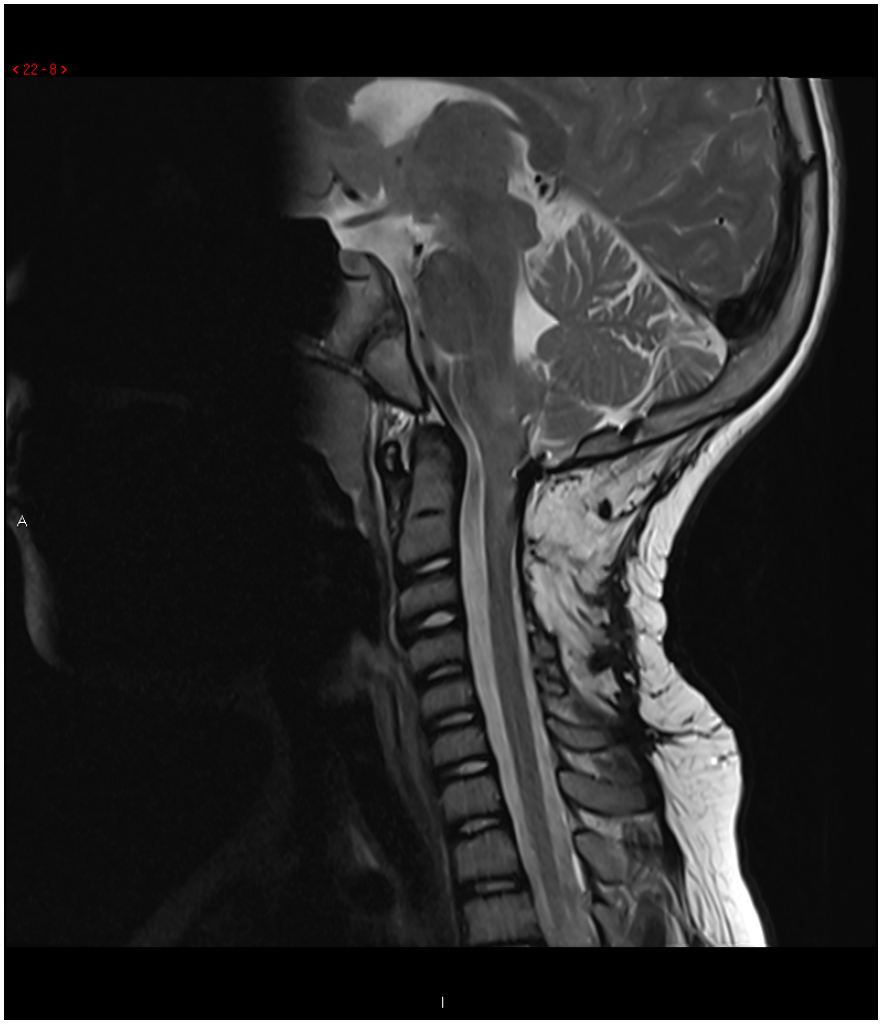

Figure 2: Images of cervical spine taken pretreatment (Upper row: A, B) and ten months following treatment (Lower row: C, D) with sagittal T2 (A, C) and post-contrast T1 images (B, D). There is an expansile infiltrative lesion involving nearly the entire medulla and extending down to the cervical cord (arrows on A). Patchy enhancement was noted on the post-contrast T1 images (arrow on B). Following treatment, there is a marked decrease in tumor size with residual high T2 signal in the cervico-medullary junction (arrow on C). Hazy post-contrast enhancement is noted at the level of the foramen magnum (arrow on D). Note surgical decompression with laminectomy at the levels of C1-C2 (asterisk on C) and edema on MRI.

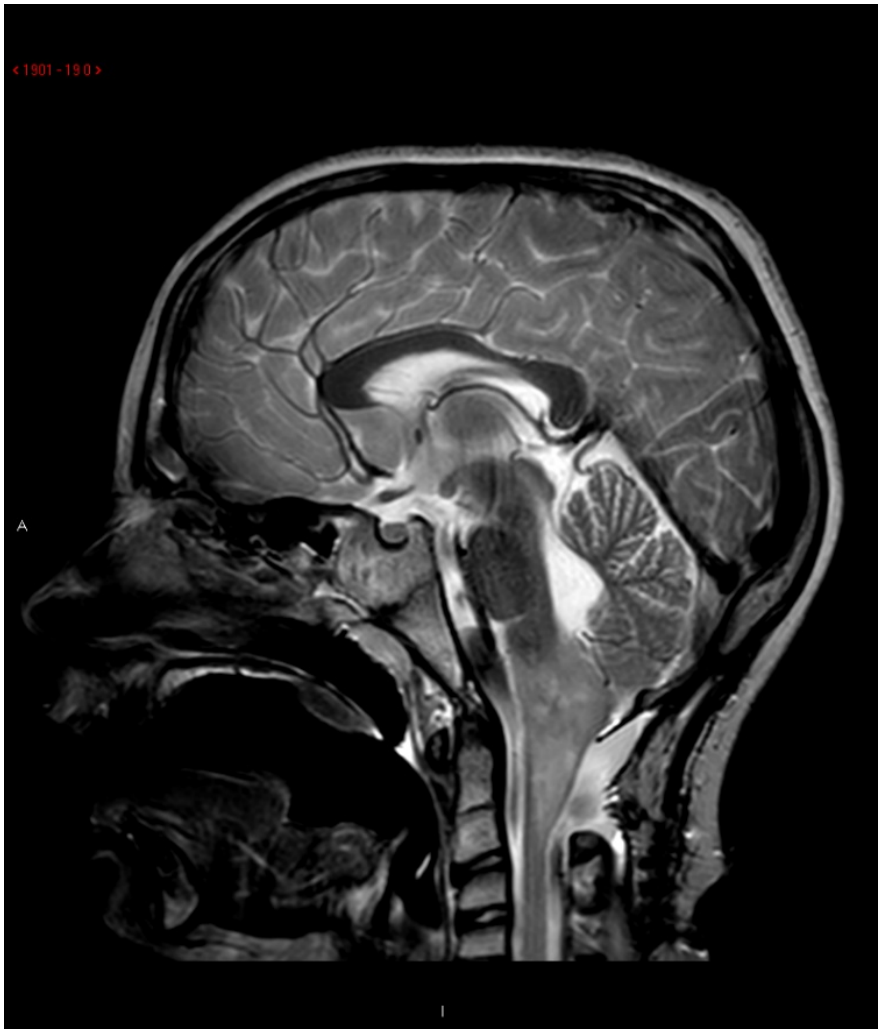

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Figure 3: Images of the brain taken pretreatment (Upper row: A, B) and five months following treatment (Lower row: C, D) with Sagittal T2 (A, C) and post-contrast T1 (B, D). There is an expansile infiltrative lesion within the medulla extending to the level of C2. Note posterior exophytic component (asterisk on A). The lesion shows patchy enhancement on post-contrast T1 images (arrow on B). Following treatment, there is still a high T2 signal within the medulla extending to the level of C2 but with marked improvement in expansion of the dorsal medulla. No enhancement is seen on post-contrast T1 images (D). Sub-occipital craniectomy with the removal of the posterior arch of C1 was performed for decompression (arrow on C).