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CASE REPORT

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Sustained response to larotrectinib in a pediatric patient with recurrent STRN3::NTRK2 fusion-positive pilocytic astrocytoma

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ABSTRACT

A 7-year-old female with recurrent midline pilocytic astrocytoma harboring a rare *STRN3::NTRK2* fusion achieved sustained near-complete radiographic and clinical response to larotrectinib, a selective TRK inhibitor. Initial subtotal resection of the midbrain/thalamic tumor was followed by progression, prompting molecular profiling that identified the *STRN3::NTRK2* fusion. Larotrectinib therapy initiated at recurrence resulted in a rapid reduction by 3 months, resolution of pontine extension by 6 months, and near-complete resolution by 15 months. This case highlights the potential of molecular diagnostics in pediatric neuro-oncology, particularly for BRAF-negative midline gliomas where NTRK fusions are rare but actionable. The durable response supports prioritizing larotrectinib over conventional chemotherapy in unresectable/progressive NTRK-driven gliomas. Routine fusion screening in BRAF-negative cases should be considered to identify candidates for targeted therapy. This report expands the known spectrum of NTRK2 partners in pilocytic astrocytoma and reinforces the use of TRK inhibitors as a treatment for molecularly defined subsets of pediatric glioma.

ARTICLE HIGHLIGHTS

- **Rare Molecular Fusion Identified:** A 7-year-old girl with recurrent midline pilocytic astrocytoma was found to have a rare STRN3::NTRK2 gene fusion, expanding the known NTRK2 fusion partners.
- **Exceptional Response to Targeted Therapy:** Initiation of larotrectinib, a selective TRK inhibitor, resulted in rapid and near-complete radiographic and clinical tumor regression, with significant improvement observed within 3–15 months of therapy.
- **Durable Remission Achieved:** The patient's tumor response has been sustained for at least 15 months, exceeding typical progression-free survival for similar pediatric CNS tumors.
- **Favorable Safety Profile:** Larotrectinib was well-tolerated, with only mild, transient side effects and no severe toxicities, which contrasts with the higher toxicity rates associated with conventional chemotherapy.
- **Clinical Improvement Paralleled Imaging:** The patient experienced notable improvements in neurological deficits, including balance, coordination, and eye alignment, alongside tumor shrinkage.
- **Implications for Treatment Paradigm:** This case supports the consideration of TRK inhibitors, such as Larotrectinib, over traditional chemotherapy for unresectable or progressive NTRK-driven gliomas in children.
- **Importance of Molecular Diagnostics:** The report emphasizes the crucial role of routine molecular screening for NTRK fusions in BRAF-negative pediatric gliomas, particularly in midline tumors where actionable fusions may be present.
- **Potential to Avoid Morbidity:** Early identification of NTRK fusions could enable the use of neoadjuvant TRK inhibitors, potentially reducing the need for high-risk surgery and the side effects of chemotherapy.

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1. Introduction

Pilocytic astrocytomas (PAs) represent the most common pediatric glioma with an incidence of 0.8 per 100,000 individuals [1,2]. PAs are often found in the cerebellum and supratentorial regions, making them amenable to complete surgical resection, which can be considered curative [3]. However, deep midline PAs pose unique therapeutic challenges due to their anatomic inaccessibility and proximity to critical neurovascular structures [4]. Consequently, surgical resection is often limited to subtotal resection, which increases the propensity for recurrence [5].

While BRAF alterations drive the vast majority of cases, on rare occasions (<1%), NTRK fusions have also been shown to drive oncogenesis. NTRK positive/BRAF negative PAs are molecularly distinct subsets among which NTRK2 rearrangements are exceptionally uncommon [6]. Current literature contains only isolated reports of NTRK2 fusion partners such as PML and ATG16L1 [7,8].

The development of selective TRK inhibitors, such as Larotrectinib, has revolutionized the management of NTRK-fusion cancers, demonstrating unprecedented response rates across a wide range of solid tumors [9]. However, clinical experience specific to pediatric NTRK2-driven gliomas remains limited to single-case reports [7,10]. This report details the successful use of larotrectinib to treat recurrence in a child with STRN3::NTRK2 fusion-positive pilocytic astrocytoma. We provide longitudinal imaging and clinical outcome data, contextualizing the findings within the evolving paradigm of molecularly targeted neuro-oncology.

2. Case presentation

2.1. Clinical history and initial management

A previously healthy 7-year-old female presented in July 2023 with progressive headaches, diplopia, and left-sided weakness over 2 years. Initial neuroimaging revealed a 4 cm heterogeneously enhancing midbrain mass involving the right thalamus, causing obstructive hydrocephalus and cerebellar tonsillar herniation (Figure 1(A and B)). Following endoscopic third ventriculostomy complicated by biopsy-related hemorrhage, the patient underwent right occipital transtentorial resection, achieving near-total tumor removal (Figure 1(B and C)). Histopathology confirmed a WHO Grade 1 pilocytic astrocytoma, while molecular profiling through a Mayo Clinic send-out lab test, NONCP (Neuro-Oncology Expanded Gene Panel with Rearrangement), revealed an STRN3::NTRK2 fusion with concurrent chromosomal imbalances disrupting STRN3 (Figures 2(A and B)) [11].

Postoperative recovery was complicated by left CN III/IV palsies and hemiparesis requiring intensive rehabilitation. Surveillance MRI at three months revealed interval progression of the residual tumor, measuring $2.3 \times 1.8 \times 2.8$ cm, with new pontine extension, prompting initiation of Larotrectinib 100 mg twice daily for 30 days (Figures 3(A and B)). Initial side effects included fatigue, nausea, decreased appetite, swelling in the feet and legs, and dizziness. However, these symptoms subsided with time. No other systemic toxic effects were identified.

2.2. Treatment response and clinical course

Serial MRI evaluations at 3-month intervals documented progressive tumor regression during larotrectinib therapy (Figure 3(C and D)). Baseline imaging showed an expansile T2/FLAIR signal involving the midbrain, thalamus, and pons with patchy enhancement. At 3 months, a reduction in FLAIR volume accompanied a decrease in enhancement, followed by an additional volumetric decrease at six months with resolution of pontine involvement. Twelve-month imaging demonstrated stable minimal residual T2 hyperintensity without enhancement, progressing to near-complete resolution of signal abnormalities by 15 months, with only blood degradation products remaining in the surgical bed (Figure 3(E and F)). Most recent imaging, 18 months post-procedure, shows stable residual T2/FLAIR volume (Figure 3(Gand H)). Clinical improvement paralleled radiographic response with improvements in balance, coordination, and eye alignment.

3. Discussion

3.1. NTRK mutations in pediatric astrocytoma

NTRK fusions are rare oncogenic drivers in pediatric PA, occurring in <1% of cases [6,12,13]. Reported fusion partners include, ATG16L1, NACC2, GKAP1, SPECC1L, HOOK3, and KIF5A [10,14–16]. These fusions constitutively activate MAPK and PI3K pathways, promoting tumorigenesis [10,16]. NTRK2 fusions, specifically, have been shown to be enriched in non-cerebellar midline PAs, and NTRK2 alterations are almost exclusively observed in central nervous system tumors [6,17].

Larotrectinib, a selective TRK inhibitor, has demonstrated efficacy in pediatric NTRK-fused PAs, achieving sustained radiographic and clinical responses in case

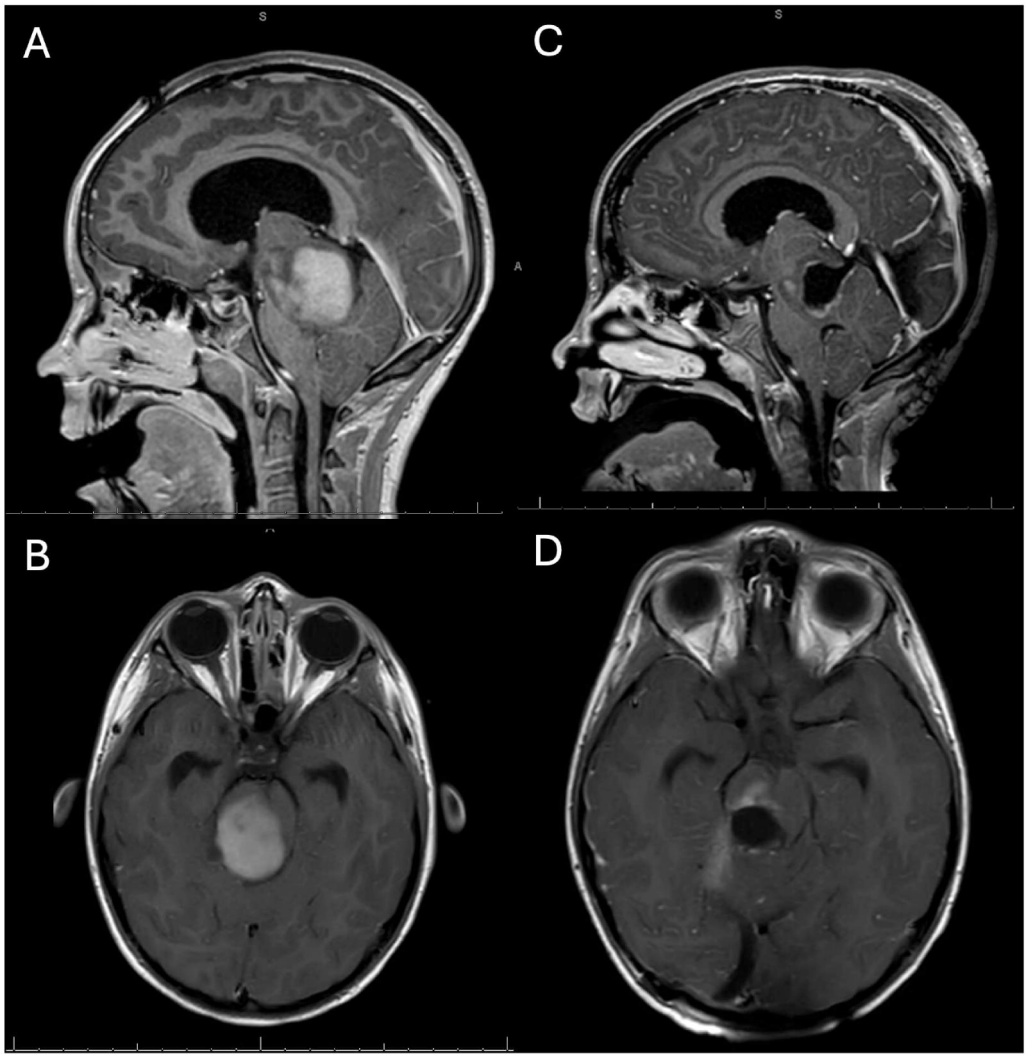

Figure 1. (A and B) Preoperative 4 cm heterogenous midbrain mass with obstructive hydrocephalus. Sagittal and Axial view. (C and D) Post-operative imaging showing near complete resection. Sagittal and axial view.

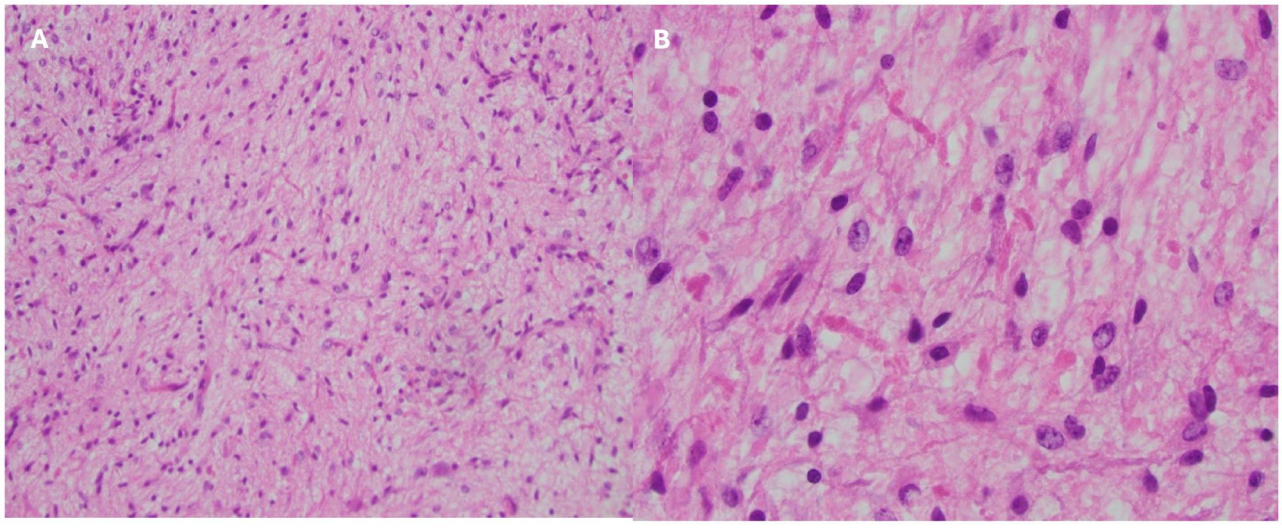

Figure 2. (A and B) Hematoxylin and eosin staining showing classical histological appearance of a WHO grade I pilocytic astrocytoma (20× and 60×).

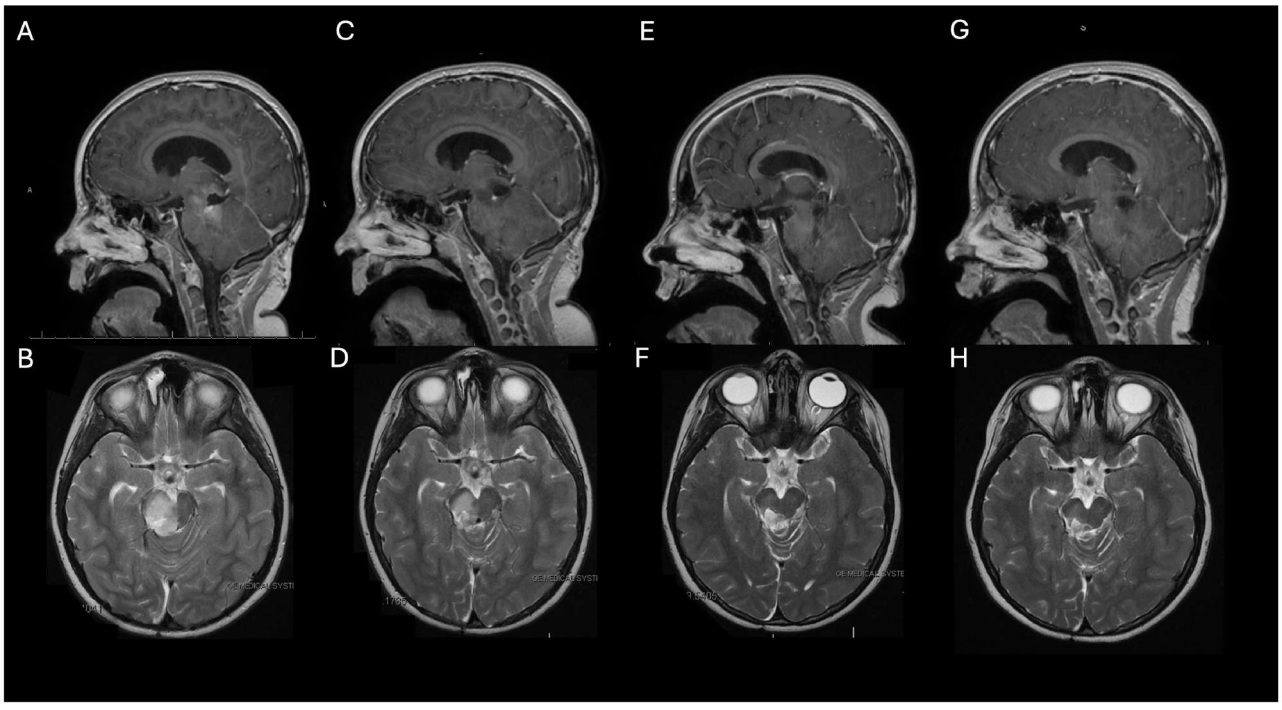

Figure 3. (A and B) Radiographic evidence of progression. Sagittal and Axial view. (C and D): Partial response after 3 months of Larotrectinib. Sagittal and Axial view. (E and F): Near-complete resolution at 15 months. Sagittal and Axial view. (G and H) Most recent imaging at 18 months showing radiographic stability.

reports. In one patient with ATG16L1::NTRK2 fusion, treatment with Larotrectinib resulted in complete remission after 8 months [10]. Adjuvant larotrectinib has also been used post-resection in NACC2::NTRK2 gliomas to prevent recurrence [17]. In addition to efficacy, the favorable toxicity profile of TRK inhibitors makes them an attractive alternative to traditional chemotherapy regimens.

3.2. Molecular characteristics and therapeutic response

This case exemplifies the critical role of molecular diagnostics in guiding precision oncology for pediatric gliomas. The identification of an STRN3::NTRK2 fusion expands the reported spectrum of oncogenic drivers in BRAF-negative pilocytic astrocytomas [6,13,14]. Functional studies of NTRK fusions in other pediatric gliomas have demonstrated that the activation of the MAPK and PI3K pathways serves as the primary oncogenic driver [18]. This pathophysiology makes larotrectinib, which inhibits TRKb autophosphorylation and downstream oncogenic cascade signaling, an attractive treatment modality [14].

The rapid radiographic response observed in this patient, FLAIR volume reduction within three months (Figure 4), aligns with pharmacokinetic data from pediatric trials demonstrating larotrectinib's central nervous system penetration [19]. This is in contrast to the historically limited success rates for chemotherapy in progressive unresectable midline gliomas, which typically show partial response rates of 24–35% with carboplatin/vincristine regimens [20]. The near-complete resolution of pontine extension by 6 months further supports larotrectinib's ability to target infiltrative tumor components, a feature particularly advantageous in anatomically complex brainstem gliomas.

3.3. Impact of NTRK2 fusion partners

Emerging evidence suggests that the specific identity of *NTRK2* fusion partners may influence clinical behavior and treatment outcomes in CNS tumors, though data remain limited [6,12]. Pediatric gliomas with *NTRK2* fusions exhibit distinct molecular patterns and prognoses compared to tumors with *NTRK1* or *NTRK3* fusions, with *NTRK2* fusions exclusively observed in CNS tumors such as low-grade gliomas (LGGs) [6].

While our case of STRN3::NTRK2 fusion represents a novel variant, the response profiles are similar to those from published cases with structurally similar partners, like GKAP1 and ATG16L1 [7,10]. The sustained remission in this patient at 15 months parallels outcomes reported for ATG16L1::NTRK2 gliomas, where complete responses were maintained for 22 months. Similarly, there appears to be a difference in treatment

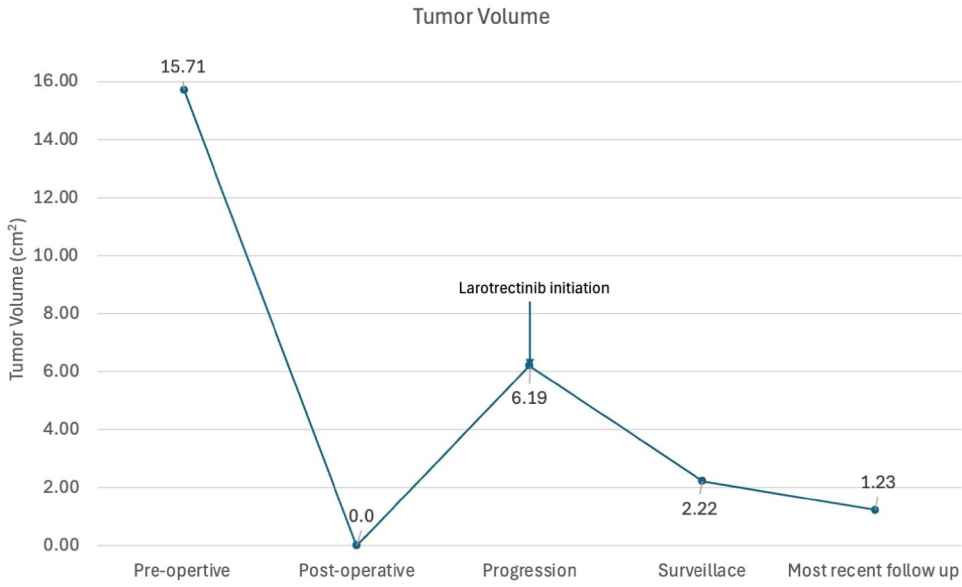

Figure 4. Changes in tumor volume, based on radiological changes, across treatment course.

durability amongst the NTRK1, NTRK2, and NTRK3 subtypes, with resistance mutations mostly documented in NTRK1 and NTRK3 [21]. However, given the limited data, it is not possible to conclusively determine if this difference is reflective of isoform differences between the TRK enzymes or a statistical byproduct of the rarity of *NTRK2*-based fusions [9,22].

3.4. Durability and resistance considerations

The patient's ongoing response at 15 months exceeds the median progression-free survival reported in pediatric TRK-CNS cohorts (14–18 months) [21,23]. However, acquired resistance remains a concern, with studies showing resistance mutations emerging in 20–30% of TRK inhibitor-treated patients [21,24]. While on-target resistance, involving mutations in the inhibitor binding site, is the most common driver of resistance, prolonged TRK inhibition has been shown to drive off-target resistance mechanisms [21]. In this context, the absence of concurrent BRAF/FGFR1 alterations in the present case likely mitigated the risk of off-target resistance and contributed to the depth and durability of the response seen. However, given the limited long-term data on larotrectinib treatment on this molecular subset, proactive surveillance remains critical for early identification of resistance.

3.5. Clinical practice implications

For recurrent/progressive PAs in pediatric patients that are not amenable to gross total resection, the conventional treatment paradigm typically involves chemotherapy, with regimens such as carboplatin and vincristine or vinblastine monotherapy. Radiation therapy may be considered for children older than 5 years, but it is often delayed to minimize neurocognitive side effects. This case supports the use of NTRK inhibitors prior to the use of chemotherapy for the management of recurrence or progression. In addition to the favorable safety profile of NTRK inhibitors, preclinical models suggest prior alkylator therapy may accelerate resistance through mutagenic stress [25].

The favorable toxicity profile observed in this case aligns with safety data from the SCOUT trial, where only 17% of pediatric patients experienced grade 3 or 4 toxicities [19]. This contrasts sharply with chemotherapy regimens, which have shown grade 3/4 cytopenias in 20–50% of patients (depending on the regimen) [26–28]. For midline gliomas where biopsy risks neurological morbidity, molecular analysis for NTRK fusions could enable trials of neoadjuvant TRK inhibitors, potentially reducing surgical morbidity and avoiding the toxic effects of conventional chemotherapy. Long-term follow-up of this patient will provide valuable insights into late recurrence patterns and neurocognitive outcomes, which are essential data given TRKb's role in neuronal development [23].

4. Conclusion

The sustained radiographic and clinical response to larotrectinib in this STRN3::NTRK2 pilocytic astrocytoma case highlights the transformative potential of molecularly targeted therapy in pediatric neuro-oncology. While long-term outcomes require further

study, this report strengthens the rationale for routine NTRK fusion screening in BRAF-negative gliomas, particularly for unresectable midline tumors, and supports larotrectinib as first-line therapy for unresectable/progressive NTRK2-driven tumors. Prospective registries tracking resistance patterns and extended follow-up will further optimize management strategies for this rare molecular subset.

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