NTRK Fusion-Positive Low-Grade Glioma in The Spine: A Case Report and Review of Literature

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Introduction

Nearly 40% of pediatric CNS tumors are low-grade gliomas (LGGs), a subgroup of heterogeneous, slow-growing tumors.(1) In fact, pediatric intramedullary spinal cord LGGs are very rare.(2) Recently, tumor diagnosis and prognostic evaluation, as well as therapeutic management, have been addressed by molecular profiling, which become significant for optimal patient management.(3–7) Moreover, there is recent attention on the neurotrophic tropomyosin receptor kinase (NTRK) gene alterations, NTRK is a family of genes (NTRK-1, NTRK-2, and NTRK-3) encoding for the tropomyosin receptor kinase (TRK-A, TRK-B, and TRK-C).(8) NTRK gene plays a role in the growth, differentiation, and survival of neurons. (9,10)

NTRK fusions have been known to be involved in many adolescent and pediatric cancers.(11) However, NTRK-2 fusion is majorly involved in pediatric patients.(12) It should be noted that only less than 1% of tumors are thought to contain NTRK fusion (13,14) and 0.55 to 2% of gliomas/neuroepithelial tumors contain NTRK.(13–18) Despite the rarity of our present case, the literature highlighted the potential clinical benefits of using targeted therapy (e.g., Larotrectinib) in tumors containing NTRK fusion.(19,20) Larotrectinib (LOXO-101) is a highly selective inhibitor of TRKA, TRKB, and TRKC administered orally.(21) Though, the efficacy of Larotrectinib has not been sufficiently defined yet.

In this study, we report a case of pediatric intramedullary spinal cord low-grade gliomas with NTKA fusion, a long (fourteen-month) follow-up. Our patient provided a consent form and agreed to the publication of this report.

Case history / examination

A 10-year-old female patient was readmitted to our facility with a prior medical history of an intramedullary spinal cord lesion for which she had undergone tumor debulking at a private hospital in July 2021. The eventual histopathological evaluation identified the lesion as diffuse astrocytoma.

In late October 2021, the patient exhibited severe upper back pain and exhibited progressive weakness in her lower extremities, which was accompanied by an unsteady gait and difficulty ascending stairs, significantly impeding her daily activities. These developments necessitated urgent hospital admission. Neurological examination identified a paraparesis, rated at 3 out of 5 in severity.

Conclusions and Results (outcome and follow-up)

In April 2022, the patient returned to the hospital due to recurrent falling incidents and an unstable gait that began 10 days prior, alongside low back pain persisting for two days. Clinical evaluations indicated

lower limb weakness, left-sided lower limb numbness, decreased sensation to light touch more pronounced on the left side, difficulty standing, reduced or absent lower limb reflexes, and a positive Romberg's sign. MRI of the spine demonstrated notable enlargement and extensive expansion of the intramedullary lesion, as shown in Figure 2. Treatment was initiated with dexamethasone, administered orally at a dosage of 4 mg every eight hours for five days. This was followed by the introduction of the targeted therapy Larotrectinib, dosed at 100 mg/kg orally, twice daily. The patient exhibited clinical improvement two days post-initiation of Larotrectinib, despite the presence of a positive clonus reflex. Subsequent MRI evaluation, 34 days after starting treatment, showed a decrease in the spinal cord lesion and expansion. However, Larotrectinib treatment was halted for one month due to supply issues but was then resumed as previously.

In August 2022, the patient experienced a decline in her condition, presenting with back pain and worsening weakness in the lower limbs, necessitating hospital admission. MRI displayed a considerable increase in the size of the spinal cord's intramedullary lesion, alongside significant expansion and edema, as shown in Figure 3. Consequently, the decision was made to recommence treatment with Larotrectinib. A follow-up MRI conducted in December 2022 demonstrated a mixed response to the treatment, with the primary feature being a mild progression of the intramedullary mass.

At the onset of January 2023, the patient was brought to the emergency room, reporting a two-week history of ataxia and a sensation of heaviness in her lower limbs, accompanied by several non-injurious falls. Her condition had deteriorated to the point where she required assistance to walk. Clinical examination revealed lower limb weakness and a reduced sensation below the T10 level. Subsequent MRI with contrast highlighted the further recurrence of disease progression in the spine and infratentorial regions. As a therapeutic intervention, craniospinal irradiation (CSI) was administered to the patient. The CSI treatment involved the utilization of the 6MV-photon Volumetric Modulated Arc Therapy (VMAT) technique. The treatment protocol consisted of a total dose of 54Gy, delivered in 20 fractions, with an additional boost phase of 18 Gy specifically targeting the infratentorial and spinal regions. Following the completion of the treatment, the patient reported the occurrence of dysphagia and a perceptible alteration in the taste of food. In addition, dexamethasone was administered orally at a dosage of 4 mg/kg every six hours for a duration of 14 days to alleviate symptoms.

By the end of January 2023, after tapering of Dexamethasone dosage, the patient's condition worsened, manifesting as increased lower limb weakness and balance issues, alongside a bilateral decrease in lower limb sensation. An MRI of the brain disclosed a new leptomeningeal lesion affecting the fourth ventricle and the anterior surface of the left cerebellar hemisphere, as indicated in Figure 4.

In February 2023, after a total duration of ten months on Larotrectinib, the treatment was discontinued. Concurrent administration of dexamethasone led to an improvement in the patient's gait. Due to the ongoing progression of the spinal lesion as indicated by MRI and suspicions of a high-grade transformation, a biopsy of the intramedullary thoracic lesion was performed. Post-surgical outcomes revealed considerable right lower limb weakness, which was more pronounced than on the left; this condition showed improvement a few days later. Subsequent postoperative MRI demonstrated a reduction in tumor burden with a documented 34% resection of the lesion and associated edema. Histological examination showed no signs of high-grade transformation, maintaining consistency with previous samples. Additionally, Bevacizumab was incorporated into the treatment regimen.

In March 2023, the patient commenced a new chemotherapy cycle, adopting a regimen comprising vincristine and carboplatin, as outlined in The Children's Oncology Group Protocol A9952, intended for maintenance until August. During this period, further molecular assessment was conducted using the OncoRisk Expanded approach, which encompasses a Next-Generation Sequencing (NGS) panel analyzing 96 genes, including Copy Number Variations (CNVs). This extensive genetic analysis revealed no pathogenic variants that could explain the clinical phenotype observed in the patient. This is a twenty-three-month follow-up.

Discussion:

Outcome of Larotrectinib

In $\frac{1}{2}$ phase clinical trial studying the use of Larotrectinib in pediatric NTRK fusion-positive solid tumors, out of the fifteen patients who were evaluated, fourteen showed a positive response according to the investigator's assessment. 26.6% of the cases showed a complete response, a partial response in 66.6% of the cases, and stable disease in 6.6% of the cases after an initial partial response.(23) Another clinical trial investigated the effectiveness of Larotrectinib in NTRK fusion-positive solid tumors and found that the drug demonstrated rapid, potent, and long-lasting antitumor activity in both children and adults. The trial reported a complete response in 13% of the patients, a partial response in 62%, stable disease in 13%, progressive disease in 9%, and 4% of the cases were unable to be evaluated due to early withdrawal from the study.(10) Additionally, Larotrectinib shows a median time of response of 1.8 months in solid tumors of adults and children.

In phase 1–2 clinical trial, two children with locally advanced tumors showed enough tumor shrinkage during Larotrectinib treatment, and both remained progression-free after 4.8 and 6.0 months of follow-up, respectively. In addition to a study, a median of six cycles of Larotrectinib was given to five children with locally advanced TRK fusion sarcomas, and all patients achieved partial response prior to surgical resection.(11,21,28)

Regarding a study that was conducted in the Children's Hospital of Philadelphia, University of Pennsylvania they mentioned their own outcomes. Larotrectinib and Entrectinib have shown antitumor effects for both primary CNS tumors and solid tumors reporting a case of SPECC1L:NTRK3 fusion that achieved complete tumor regression.(11) In another study of nine patients with primary CNS tumors treated with NTRK inhibitors, disease control was observed in all evaluable patients with stable disease in seven patients.(23) Also, a case report of pediatric low-grade glioma with GKAP1-NTRK2 fusion reveals a significant improvement after Larotrectinib clinically and radiologically by the assessment of Neuro-oncology (RANO) criteria. It is worth mentioning that there were no side effects over fourteen months of follow-up.(27)

In an earlier study, a case of LLG and CLIP2:NTRK2 fusion was treated with the TRK inhibitor larotrectinib, which resulted in a 40% reduction in volume that was detectable on magnetic resonance 54 days after the therapy began. The reduction in radiological volume was accompanied by significant clinical improvement and no drug-related toxicity. Unfortunately, tumor progression and clinical decline were discovered after 22 months of targeted therapy. The patient died five months later as a result of tumor progression to the brainstem.(25) This case can be considered as one of the cases of the treatment resistance development that has been proposed suggesting the probability of first-generation inhibitors resistance. At least two broad resistance mechanisms have been identified. The first is associated with off-target alterations that reactivate one of the cellular pathways associated with NTRK fusions, typically the mitogen-activated protein kinase (MAPK). In fact, the MAPK signaling cascade can be activated by a variety of signal transducers unrelated to NTRK. This resistance mechanism includes the acquisition of BRAFV600E or KRASG12D mutations, as well as Mesenchymal-Epithelial Transition (MET) amplification. The second tumor escape strategy (so-called on-target resistance) is linked to NTRK fusion protein point mutations (i.e., solvent front, gatekeeper, and xDFG mutations), which prevent drug binding. Next-generation NTRK inhibitors (e.g., repotrectnib—TPX-0005, LOXO-195-BAY2731954) have been developed in this regard, and have shown promising efficacy in targeting these mutated fusion proteins.(24)

Testing for NTRK Fusions

Starting with a chromosomal rearrangement, NTRK oncogenic activation necessitates translation of the fusion gene and expression of the chimeric TRK protein. To determine if a tumor has an NTRK fusion, various laboratory assays can be employed. The DNA status can be investigated using fluorescence in-situ hybridization (FISH) and DNA-based next-generation sequencing (NGS), while evaluating the transcribed RNA, reverse transcription-polymerase chain reaction (RT-PCR), real time-PCR, and RNA-based NGS analyses can be utilized. These methods examine the RNA molecules produced by the tumor. Finally, the protein product can be directly evaluated using immunohistochemical staining (IHC). This technique allows for the visualization and analysis of the chimeric TRK protein. These laboratory assays collectively help in determining whether a tumor has undergone NTRK fusion and activation.(24)

Malignant transformation of low-grade glioma

In children, the most common benign tumors in the central nervous system are called LGGs. Unlike LGGs in adults, LGGs in children progress to malignancy, with an incidence rate of up to 10%. This transformation can sometimes occur even without adjuvant radiation therapy.

There have been two cases reported in India where LGGs in children transformed into malignant tumors. In one case, a 7-year-old girl had a tumor in the left temporal region, which was initially diagnosed as a benign pilocytic astrocytoma (WHO grade I). However, after eight years, the tumor transformed into a malignant form. In the second case, a 10-year-old boy had a tumor in the left frontoparietal region, initially diagnosed as a benign ganglioglioma (WHO grade I). After 10 months, the tumor progressed into a more severe form called anaplastic ganglioglioma (WHO grade III).(27)

These cases, along with other studies on the genetic factors involved in the malignant transformation of LGGs in children, highlight the need to identify patients at risk of transformation early on. This will allow for a more aggressive treatment approach to be taken. A study published in 2020 emphasized the limited treatment options for high-grade pediatric gliomas and the potential harmful effects of radiotherapy in children. Therefore, regular screening and follow-up are crucial in preventing the transformation of LGGs in children.(24)

Conclusion

The recognition of NTRK as a potential oncogene is now dated, the proper understanding of the specific mechanisms involved and their appreciation as a potential therapeutic target is far more recent. NTRK inhibitors have shown high efficacy in multiple NTRK-driven cancers shining the concept of "targeted therapy".

This case illustrates the response seen in pediatric intramedullary spinal cord LGGs with NTKA2 fusion treated with Larotrectinib. This case's findings are similar to the findings of a clinical trial that was conducted for 24 patients, highlighting the potential of targeted therapies in pediatric patients when oncogenic drivers can be identified and selective inhibitors are available. Accordingly, our case suggests the use of the multilayer diagnosis integrating histopathology and molecular genetics analysis could have significant prognostic implications.

Abbreviations

CNS: Central Nervous System

NTRK: Neurotrophic Tyrosine Receptor Kinase

TRK: Tropomyosin Receptor Kinase

LGGs: Low-Grade Gliomas

FISH: Fluorescence In Situ Hybridization

NGS: Next-Generation Sequencing

CNVs: Copy Number Variations

CSI: Craniospinal Irradiation

VMAT: Volumetric Modulated Arc Therapy

MAPK: Mitogen-Activated Protein Kinase

RT-PCR: Reverse Transcription Polymerase Chain Reaction

References

1. Qaddoumi I, Sultan I, Gajjar A: Outcome and Prognostic Features in Pediatric Gliomas: a Review of 6212 Cases From the SEER Database. Cancer 115: 5761-5770, 2009. 2. Ochroch EA, Fleisher LA: Evaluating pediatric spinal low-grade gliomas—a 30-year retrospective analysis. Anesthesiology 105: 643-644, 2019. 3. Fussey JM, Vaidya B, Kim D, Clark J, Ellard S, Smith JA: The role of molecular genetics in the clinical management of sporadic medullary thyroid carcinoma: A systematic review. Clin Endocrinol (Oxf) 91: 697-707, 2019. 4. Soiza RL, Donaldson AIC, Myint PK: Molecular targeted therapy of BRAF-mutant colorectal cancer. Ther Adv Vaccines 9: 259-261, 2018. 5. Chen DS, Mellman I: Elements of cancer immunity and the cancer-immune set point. Nature 541: 321-330, 2017. 6. Herbst RS, Morgensztern D, Boshoff C: The biology and management of non-small cell lung cancer. Nature 553: 446-454, 2018. 7. Jørgensen JT: A paradigm shift in biomarker guided oncology drug development. Ann Transl Med 7: 148, 2019. 8. Rubin JB, Segal RA: Growth, survival and migration: the Trk to cancer. Cancer Treat Res 115: 1-18, 2003. 9. Laetsch TW, DuBois SG, Mascarenhas L, Turpin B, Federman N, Albert CM, et al: Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol 19: 705-714, 2018. 10. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al: Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children. N Engl J Med 378: 731-739, 2018. 11. Zhao X, Kotch C, Fox E, Surrey LF, Wertheim GB: NTRK Fusions Identified in Pediatric Tumors: The Frequency, Fusion Partners, and Clinical Outcome. J Clin Oncol 37: 1234-1242, 2019. 12. Nakagawara A: Trk receptor tyrosine kinases: A bridge between cancer and neural development. Cancer Lett 169: 107-114, 2001. 13. Amatu A, Sartore-Bianchi A, Siena S: NTRK gene fusions as novel targets of cancer therapy across multiple tumour types. ESMO Open 1: e000142, 2016. 14. Torre M, Vasudevaraja V, Serrano J, Delorenzo M, Malinowski S, Blandin AF, et al: Molecular and clinicopathologic features of gliomas harboring NTRK fusions. Acta Neuropathol Commun 8: 1-14, 2020. 15. Okamura R, Boichard A, Kato S, Sicklick JK, Bazhenova L, Kurzrock R: Analysis of NTRK Alterations in Pan-Cancer Adult and Pediatric Malignancies: Implications for NTRK-Targeted Therapeutics. JCO Precis Oncol 2: 1-20, 2018. 16. Johnson K, Barragan J, Bashiruddin S, Smith CJ, Tyrrell C, Parsons MJ, et al: TRK Fusions are Enriched in Cancers with Uncommon Histologies and the Absence of Canonical Driver Mutations. Physiol Behav 176: 139-148, 2017. 17. Ferguson SD, Zhou S, Huse JT, De Groot JF, Xiu J, Subramaniam DS, et al: Targetable Gene Fusions Associate With the IDH Wild-Type Astrocytic Lineage in Adult Gliomas. Mol Cancer Res 18: 512-521, 2020. 18. Gatalica Z, Xiu J, Swensen J, Vranic S: Molecular characterization of cancers with NTRK gene fusions. Mod Pathol 32: 147-153, 2019. 19. Solomon JP, Linkov I, Rosado A, Mullaney K, Rosen EY, Frosina D, et al: NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. Mod Pathol 33: 38-46, 2020. 20. Yoshihara K, Wang Q, Torres-garcia W, Zheng S, Vegesna R, Kim H, et al: The landscape and therapeutic relevance of cancer-associated transcript fusions. J Clin Oncol 34: 4845-4854, 2016. 21. DuBois SG, Laetsch TW, Federman N, Turpin BK, Albert CM, Nagasubramanian R, et al: The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas. Cancer 124: 4241-4247, 2018. 22. Deland L, Keane S, Olsson T, Sjögren H, Fagman H, Øra I: Discovery of a rare GKAP1-NTRK2 fusion in a pediatric low-grade glioma, leading to targeted treatment with TRK-inhibitor larotrectinib. Cancer Biol Ther 22: 184-195, 2021. 23. Drilon A: TRK inhibitors in TRK fusion-positive cancers. Ann Oncol 30: VIII23-VIII30, 2019. 24. Gambella A, Senetta R, Collemi G, Vallero SG, Monticelli M, Cofano F, et al: NTRK fusions in central nervous system tumors: A rare, but worthy target. Int J Mol Sci 21: 1-24, 2020. 25. Adela M, Ales V, Petr B, Katerina V, David S, Lucie S, et al: Integrated genomic analysis reveals actionable targets in pediatric spinal cord low-grade gliomas. Acta Neuropathol Commun 10: 1-11, 2022. 26. Range K, MD, Moser YA: TRKing down an old oncogene in a new era of targeted therapy. Bone 23: 1-7, 2012. 27. Avinash K, Thakar S, Aryan S, Ghosal N, Hegde A: Malignant Transformation of Pediatric Low-grade Gliomas: Report of Two Cases and Review of a Rare Pathological Phenomenon. Neurol India 67: 1100-1106, 2019. 28. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, et al: Efficacy of Larotrectinib in TRK Fusion–Positive Cancers in Adults and Children. N Engl J Med 378: 731-739, 2018.

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