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Brief Communication

Response to entrectinib in a malignant glioneuronal tumor with ARHGEF2-NTRK fusion

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Glioneuronal tumor (GNT) is a rare tumor. We previously reported a case of high-grade GNT with Rho/Rac guanine nucleotide factor 2 (*ARHGEF2*)-neurotrophic tropomyosin receptor kinase (*NTRK*)*1* fusion and emphasized the importance of complementary molecular analysis.[1] MRI at follow-up showed tumor progression. A cancer gene panel test was performed, and the presence of the *ARHGEF2-NTRK1* fusion gene was confirmed. Treatment with entrectinib, an inhibitor of NTRK, was started. MRI follow-ups revealed dramatic responses. However, the patient reported severe general fatigue, and the dose was decreased following the reduced drug protocol. This case highlights the necessity of determining an optimal dose and further profiling the side effects of NTRK inhibitors.

A right-handed 14-year-old Asian female presented with headaches in 20XX. MRI detected 2 cystic lesions bilaterally in the frontal areas with surrounding edema (Figure 1A and B). She had removal of the larger left tumor and the patient underwent left frontal craniotomy twice (Figure 1C); the patient received extended local field irradiation (60Gy/30fr) and temozolomide (13 cycles in total). Pathological examinations diagnosed high-grade GNT with vascular growth and a 20% Ki-67 index. RNA sequencing identified an *ARHGEF2* (encoding Rho/Rac guanine nucleotide factor 2)-*NTRK1* fusion gene. MRI follow-up revealed rapid progression, with tumor progression observed 2 years after the first operation (Figure 1D). A cancer gene panel test using FoundationOne CDx was performed, and the *ARHGEF2-NTRK1* fusion gene was confirmed. We used entrectinib because it had been approved in Japan at the time of treatment. MRI follow-ups 1 month later and 3 months later revealed dramatic responses (Figure 1E and F). The lesion on the left disappeared and the lesion on the right shrank. However, the patient's general fatigue was severe, and the dose was decreased following the reduced drug protocol. One month later, the dose was decreased to 300 mg/day, and 2 months later, the dose was reduced to 200 mg/day 2 days/week. There was no other drug approved in Japan for NTRK inhibitor except for entrectinib; thus, we continued to use entrectinib. Although the drug dose was decreased, we had to further reduce the dosage because the patient's general malaise continued. Five months later, the patient took entrectinib 100 mg/day for 1 day/2 weeks. MRI showed regrowth 6 months after starting entrectinib (Figure 1G and H).

The *NTRK* genes, *NTRK1*, *NTRK2*, and *NTRK3*, are involved in the modulation of various biological processes and cellular functions.[2] Intra- or inter-chromosomal rearrangements of *NTRK* lead to the production of fusion genes, a factor in carcinogenesis in various cancers.[2] A first-in-class tropomyosin receptor kinase (*TRK*) inhibitor, larotrectinib, was approved in 2018 by the US Food and Drug Administration (FDA) and has been increasingly used for adult and pediatric solid cancers, including central nervous system (CNS) tumors. The TRK inhibitor larotrectinib has inhibitory activity against TRKA/B/C. Entrectinib has inhibitory activity against TRKA/B/C, ROS1, and ALK. While drug penetration to the CNS is always a problem in brain tumor treatment, both entrectinib and larotrectinib have been reported to be effective for metastatic and primary brain tumors.[2,3] Recently, the efficacy and safety of larotrectinib were evaluated in patients with TRK gene fusion-positive primary CNS tumors.[3] The objective response rate (ORR) was 30% for all patients and the 24-week disease control rate

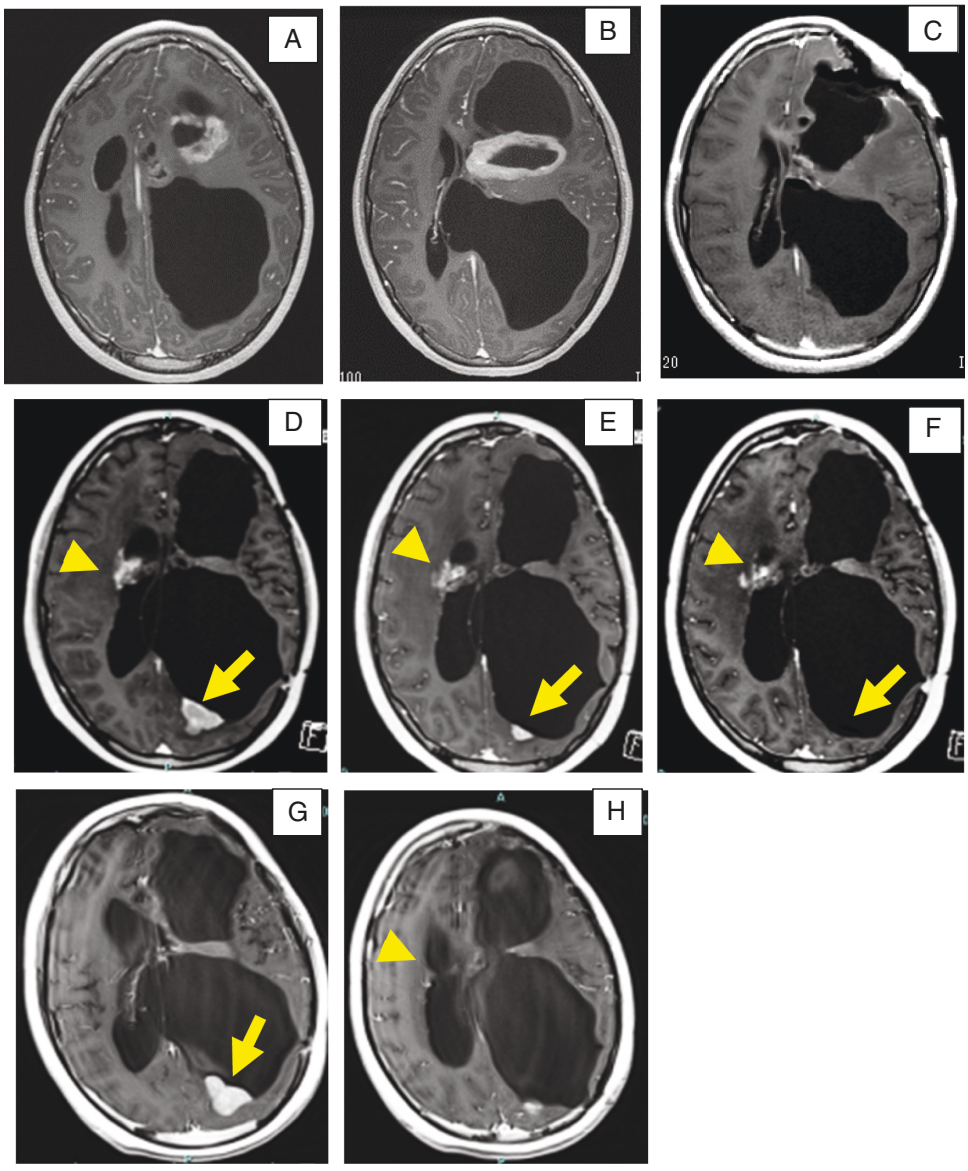

Figure 1. MRI follow-up revealed rapid progression and drastic response to entrectinib. (A, B) Baseline axial Gd-enhanced MRI image showing cystic tumors in the bilateral frontal area and hydrocephalus. (C) MRI after second op. (D) Gd-enhanced MRI showing recurred lesions in the left lateral ventricle (arrow) and the right frontal area (arrow head). Both lesions showed shrinking after the initiation of entrectinib. (E) One month after starting treatment of entrectinib. (F) Two months after starting treatment). (G, H) Six months after treatment of entrectinib, the tumor progressed in the left lateral ventricle, but the lesion in the right frontal area decreased.

was 73%. Entrectinib is used to treat ROS1-positive non-small cell lung cancer and *NTRK* fusion-positive solid tumors.[2] Four clinical trials, including the first I/Ib study in children and adolescents (STARTRK-NG), have examined entrectinib and were recently updated.[4] The median follow-up was 25.8 months, and 61.2% of patients had a complete response.[4] In 11 patients with measurable CNS disease, the intracranial ORR was 63.6% and the median intracranial duration of response was 22.1 months. The efficacy of entrectinib for *NTRK* fusion-positive brain tumors was also confirmed in our case.

The most common side effects of entrectinib include fatigue, constipation, taste disorders, edema, dizziness, diarrhea, nausea, paresthesia, breathing difficulties, anemia, and weight gain.[2] In a systematic review of the pooled analyses of entrectinib trials reported by Chu et al,[5] the second most common adverse event was fatigue (25.1% in the overall population and 27.9% in the *NTRK* fusion-positive population). In the present case, fatigue and general malaise led to dose reduction of entrectinib.

ARHGEF2-NTRK1 fusion is extremely rare. The first case of glioblastoma was reported among the 115 brain tumor formalin-fixed, paraffin-embedded (FFPE) analyses in 2014.[6] Westphalen et al examined the genomic profiling data from the FoundationCORE database[7] and from 295 676 patients only 1 case of *ARHGEF2-NTRK1*

was observed in 889 NTRK gene fusion cases. Torre et al described molecular and clinicopathologic features of gliomas harboring *NTRK* fusions and showed only 2 cases of *ARHGEF2-NTRK1* fusion, including a high-grade glioma and glioblastoma.[8] STARTRK-NG included only one *ARHGEF2-NTRK1* case, who was 24-month-old spinal glioblastoma, treated with entrectinib. The patient had stable disease and the treatment duration at data cutoff were 22.4 months.[9]

In *NTRK* fusion-positive tumors in the FoundationCORE database, *ETV6-NTRK3*-positive tumors were most common in adults (26.4%) and pediatric patients (32.7%).[7] Papusha et al reported the successful treatment of *ETV6-NTRK3*-positive infant glioblastoma with entrectinib.[10] The authors reviewed previous reports on high-grade glioma, glioblastoma, and low-grade neuroepithelial neoplasm. Treatment of these cases with larotrectinib or entrectinib was effective and well-tolerated.[10] Only 1 case showed a side effect of elevated liver function tests. Entrectinib was effective in our case with *ARHGEF2-NTRK1*; however, the side effect of fatigue was reported. These drugs might have different effects or side effects depending on the gene fusion partner. Further exploration of the effects and side effects of these drugs in fusion-positive tumors is required.

This case demonstrates the importance of complementary molecular analysis and the efficacy of NTRK inhibitor in *NTRK* fusion high-grade GNT. This case also emphasizes the necessity of deciding an optimal dose and supports the need for further profiling of side effects of NTRK inhibitors.

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