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Letter to the Editor

Two clinically distinct cases of infant hemispheric glioma carrying *ZCCHC8:ROS1* fusion and responding to entrectinib

Infant hemispheric high-grade gliomas (iHGGs) constitute a biologically and clinically distinct subgroup of pediatric HGGs. One defining hallmark of iHGG is rearrangement of receptor tyrosine kinase either *ALK*, *ROS1*, *NTRK1,2,3*, or *MET*. The *ROS1*-positive iHGGs are an exceptionally rare tumor subtype with a relatively poor prognosis.[1] The most typical *ROS1* fusion partner for such tumors is *GOPC*.[2] Here we describe two extremely rare cases of iHGG with *ROS1* fused with the Zinc Finger CCHC-Type Containing 8 (*ZCCHC8*) gene. Although these patients had major differences in clinical presentation, MRI characteristics, and histopathology, both children were successfully treated with the NTRK/ROS1/ALK inhibitor entrectinib. To date, only two *ZCCHC8:ROS1*-positive gliomas were described; one of the patients received targeted therapy.[3,4]

In our first patient, a 1-month-old female, the tumor was diagnosed as an intracranial mass on routine neurosonography. MRI demonstrated a well-demarcated left frontoparietal solid 1.5 × 1.6 × 1.7 cm mass, which had homogeneous contrast enhancement (Figure 1A). The initial choice was a watch-and-wait strategy, but in 2 months, the tumor size reached 2.6 × 2.4 × 2.9 cm. A gross-total resection was performed with minimal blood loss and no neurologic complications. Histopathological examination was consistent with HGG with epithelioid and rhabdoid features. The RNA sequencing revealed a *ZCCHC8:ROS1* fusion transcript (*ZCCHC8*: ENST00000633063.3, exon1; *ROS1*:ENST00000368508.7, exon36); the integrative diagnosis was infant-type hemispheric glioma, *ROS1*-rearranged. The patient received chemotherapy according to the BabyPOG protocol.[5] After 3 cycles of chemotherapy, MRI showed local recurrence. The patient then underwent a near-total resection and histopathological examination demonstrated similar morphologic features. We considered two ROS1 kinase inhibitors, crizotinib and entrectinib. The preference was given to entrectinib for its ability to penetrate the blood-brain barrier.[6,7] Entrectinib (supplied by Roche via a compassionate use program) was administered in 300 mg daily doses. To date, the patient remains clinically stable on entrectinib for 11 months, with no signs of recurrence on MRI and no treatment-related adverse events.

The second newborn girl presented with increasing head circumference and left hemiparesis. MRI revealed a large heterogeneous hypervascular mass in the right hemisphere, 12.5 × 10 × 9.6 cm, with cystic components and signs of intratumoral hemorrhage (Figure 1B). It was decided to proceed without a biopsy due to the risks of life-threatening hemorrhage. Chemotherapy according to the HIT-MED Guidance protocol (ClinicalTrials.gov NCT02417324) was initiated. MRI performed after 2 cycles of chemotherapy showed progressive disease, associated with neurological deterioration. A biopsy

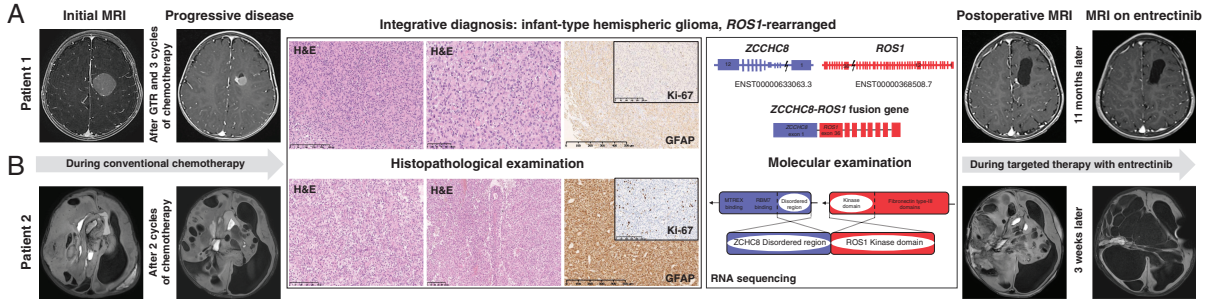

Fig. 1 Clinical course for the two cases [Patient 1-panel (A), Patient 2-panel (B)], with corresponding MRI, histopathology, immunohistochemistry (IHC), and molecular data. IHC panel included CD34, chromogranin A, EMA, GFAP, Ki-67, myelin basic protein, NeuN CC2, neurofilament, p53, S100, INI1, H3K27me3. Cells of both tumors were immunopositive for S100, GFAP, INI1, p53, H3K27me3.

was finally performed, complicated by severe bleeding. Histopathological examination revealed a glial tumor with rare astroblastic pseudorosettes. The *ZCCHC8:ROS1* fusion transcript was identified, identical to described in the first case. Entrectinib (90 mg daily) was administered as a salvage therapy. MRI performed after 3 weeks of the targeted therapy revealed a rapid dramatic response with regression of the solid component of the tumor and no apparent side effects. The patient continues on entrectinib for 5 months and is clinically stable without neurological deficits.

Only two reports on *ZCCHC8:ROS1*-positive tumors have been published, and only one was given the targeted therapy. *ZCCHC8* as a fusion partner of *ROS1* was firstly identified in a case of congenital glioblastoma; the patient died of intraoperative hemorrhage.[3] Another patient, a 4-month-old girl diagnosed with *ZCCHC8:ROS1*-positive glioblastoma, received chemotherapy, multiple resections, anti-MEK targeted therapy, and ultimately was treated with entrectinib. The patient improved neurologically and demonstrated tumor shrinkage on MRI.[4] After 11 months of the anti-ROS1 therapy, resistance occurred resulting in the fatal disease progression (Dr Ku, personal communication).

ROS1 rearrangements were described in a variety of pediatric malignancies, including HGGs, glioneuronal tumors, atypical meningioma, inflammatory myofibroblastic tumors, and pleuropulmonary blastoma.[2,7–9] The efficacy of targeted therapy against ROS1 fusion proteins was evaluated in the STARTRK-NG trial. However, only two patients with gliomas harboring *GOPC:ROS1* and *EEF1G:ROS1* fusions were enrolled in the trial; both of them demonstrated partial tumor response.[10] Additionally, two single cases of targeted therapy of *ROS1:ARCN1* and *ZCCHC8:ROS1*-rearranged gliomas represented resistance to entrectinib after 4 and 11 months of therapy, respectively.[4,6] Mechanisms of resistance may involve secondary point mutations in the ROS1 kinase domain (F2004C/I and G2032R) or collateral signaling pathway activation.[7] The resistance could theoretically be overcome by a combination of several modalities (radiation therapy, different kinase inhibitors) or next-generation ROS1 inhibitors, although further clinical testing is needed.

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Ludmila Papusha, Margarita Zaytseva, Agnesa Panferova, Alexander Druy, Andge Valiakhmetova, Anton Artemov, Ekaterina Salnikova, Alexey Kislyakov, Evgeny Imyanitov, Alexander Karachunsky, Alexey Maschan, Eugene I. Hwang, Galina Novichkova, and Roger J. Packer

Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation (L.P., M.Z., A.P., A.D., A.V., A.A., E.S., A.K.I., A.K.A., A.M., G.N.); Morozov City Children Hospital, Moscow, Russian Federation (A.K.I.); St. Petersburg Pediatric Medical University, St. Petersburg, Russian Federation (E.I.); N.N. Petrov Institute of Oncology, St. Petersburg, Russian Federation (E.I.); Division of Oncology, Children's National Hospital, Washington, DC, USA (E.I.H., R.J.P.); Brain Tumor Institute, Washington, DC, USA (E.I.H., R.J.P.); Center for Neuroscience and Behavioral Medicine, Washington, DC, USA (R.J.P.)

Corresponding Author: Ludmila Papusha, MD, PhD, Head of Department of Pediatric Neurooncology, Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Samory Mashela str., 1, Moscow 117997, Russian Federation (ludmila.mur@mail.ru).

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