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LETTER TO THE EDITOR

Pediatric diffuse leptomeningeal glioneuronal tumor: Two clinical cases of successful targeted therapy

To the Editor:

Diffuse leptomeningeal glioneuronal tumor (DLGNT) is an extremely rare disease,[1] which appears as diffuse leptomeningeal lesions[2,3] and typically harbors a KIAA1549-BRAF fusion oncogene.[4] Other alterations, such as the BRAF V600E substitution, are less common.[3] Due to the rarity of the disease, there are no standard therapeutic strategies for treatment of children with DLGNT. Here, we report two cases of successful DLGNT treatment with kinase inhibitors.

The first patient, an 8-year-old male, presented with simple absence seizure episodes. Treatment with anticonvulsant therapy resulted in temporary control of the seizure-like episodes; however, daily seizures recurred in addition to headaches, rapid visual deterioration, and significant weight loss. Neuroimaging revealed hydrocephalus and leptomeningeal enhancement along the basal cisterns, suprasellar region, posterior fossa, and spinal cord (Figure 1A). Biopsy of the temporal region pia mater was conducted along with ventriculoperitoneal shunting. Histopathological examination revealed a neuroepithelial neoplasm with diffuse leptomeningeal infiltration and prevalent ganglion cells with eosinophilic bodies. Mitotic figures, necrosis, and microvascular proliferation were not present in the specimen. Sanger sequencing revealed a nucleotide substitution, *BRAF* c.1799 T>A (V600E).

The patient was diagnosed with DLGNT and was administered carboplatin (550 mg/m^2 at weeks 1, 4, 7, and 10) and vincristine (1.5 mg/m^2 per week for 10 weeks). After 10 weeks of chemotherapy, neuroimaging indicated disease progression. In addition, there was clinical deterioration with development of pain in the lower limbs and worsening of the gait. The patient began a 24-month anti-BRAF treatment with vemurafenib 720 mg twice per day. After 8 months, MRI demonstrated complete tumor response (Figure 1B). The treatment was well tolerated with the only toxicity being a grade

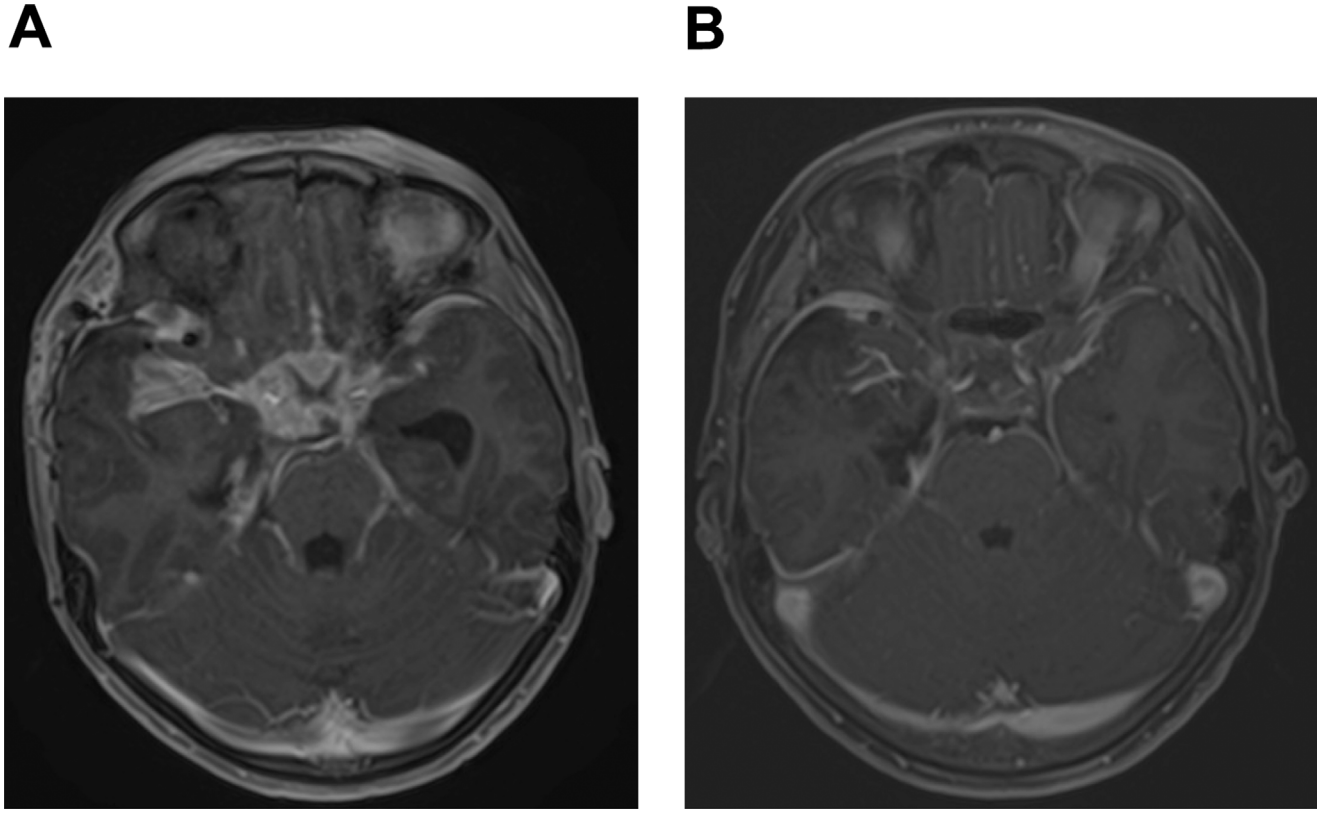

FIGURE 1 Magnetic resonance imaging, patient 1. A, Initial T1-weighted axial view of the brain shows diffuse leptomeningeal enhancement. B, T1-weighted contrast view after 8 months of anti-BRAF therapy shows complete tumor regression

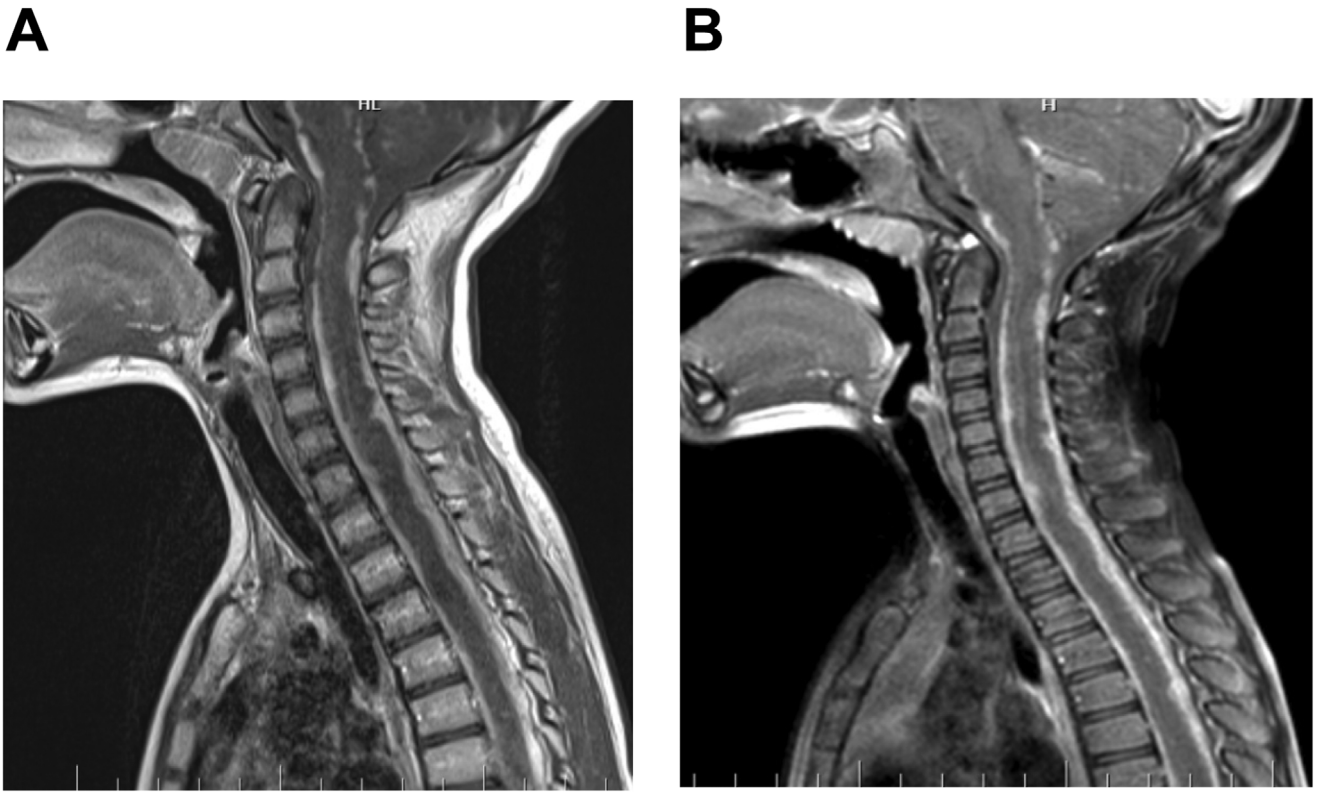

FIGURE 2 Magnetic resonance imaging, patient 2. A, Initial sagittal T1-weighted cervical images show leptomeningeal enhancement along the pia mater. B, Sagittal T1-weighted cervical images after 10 months of anti-MEK therapy show disease stabilization

l skin rash on the wrists. The child remains clinically stable after 24 months of treatment and neurologically intact with no further epileptic seizures or pain in the lower limbs and excellent quality of life.

The second patient, a 27-month-old male, presented with ataxia and vomiting. MRI revealed a diffuse lesion of the meninges with hydrocephalus. Due to the suspicion of bacterial meningitis, antibacterial treatment was administered, but no clinical improvement was seen. The patient was under close follow up without further medications; and seizures began 11 months later. Repeat neuroimaging revealed diffuse intracranial and spinal leptomeningeal enhancement (Figure 2A) with thickening of the meninges and cystic, nonenhancing T2-weighted meningeal lesions, and several intramedullary enhancing foci throughout the thoracic and upper lumbar regions. A biopsy of abnormal spinal pia mater at the L5 segment level revealed DLGNT. The oncogenic fusion transcript *KIAA1549-BRAF* (exons 15-9) was found in the tumor specimen by reverse transcriptase PCR. Considering the young age of patient, significant tumor burden, and presence of the BRAF fusion, targeted therapy with the MEK inhibitor trametinib was selected as front-line treatment. The child was administered oral trametinib 0.5 mg/day (0.032 mg/kg/day) for 24 months. Tumor stabilization was noted on the MRI (Figure 2B) 10 months after treatment initiation, and disease control has been demonstrated since month 14. The patient is doing well after 25 months of treatment, with the only toxicity being a grade 2 paronychia. He has good quality of life and attends kindergarten.

Due to the extreme rarity of DLGNT, there are no standard treatments for the disease. Accumulation of global clinical data and successful treatment results are mandatory to determine optimal treatment for these patients.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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