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Clinical Letter

A Child With Lymphangioma Due to Somatic Mutation in *PIK3CA* Successfully Treated With Everolimus

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Multiple heterogeneous segmental overgrowth disorders have been reported to be associated with somatic mutations in phosphatidylinositol-4,5-bisphospate 3-kinase, catalytic subunit alpha (PIK3CA) over the last 10 years.[1,2] The PIK3CA-related overgrowth spectrum (PROS) encompasses the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway-related overgrowth conditions, which have clinical diversity with numerous organ involvements including the central nervous system. Somatic mutations can arise during brain development, resulting in brain malformations associated with epilepsy and intellectual disability.[3]

We encountered a child with epilepsy and intellectual disability combined with cystic lymphangioma. The seven-year-old boy visited our clinic for evaluation of unprovoked seizures and cognitive impairment. He had been treated for a congenital cystic mass which had been detected before birth by antenatal sonography and confirmed by neck magnetic resonance imaging the day after birth (Fig 1A). The large cystic mass on his right anterolateral neck was diagnosed as a cystic lymphangioma; he underwent three resection surgeries but the lymphangioma eventually reappeared (Fig 1B). On suspicion of PROS referenced by the clinical diagnostic criteria suggested by experts at the recent National Institutes of Health sponsored workshop, we examined tissue obtained from the lymphangioma on the third resection surgery and whole blood for somatic mutations in *PIK3CA*. We analyzed and compared hot-spot mutations including E542K, E545K, H7047L, and H1047R in *PIK3CA* from the patient's lymphangioma tissue and leukocytes using mutant enrichment with 3′-modified oligonucleotides (MEMO)-quantitative polymerase chain reaction (Fig 2). MEMO, which we used in this child, is a simple and low-cost enrichment technique based on the use of the one MEMO primer that blocks extension of the normal allele but enables extension of the mutated allele. It can be applied in cancer mutation detection and minor mutant allele detection in patients with low-level somatic mosaicism or mitochondrial heteroplasmy because of its simplicity of performance, variability of downstream assays, excellent sensitivity, and very low probability of false positives.[4]

Regarding PROS treatment, surgical excision and conservative care, as well as treatment with small-molecule inhibitors, can be attempted using the PI3K pathway.[5] In multiple cancers, including head and neck squamous cell carcinomas, associated with the PI3K/AKT/mTOR signaling pathway, a correlation between mTOR activation and favorable prognosis was previously reported.[6]

We administered everolimus (5 mg/day), an analogue of rapamycin, for longer than six months to prevent regrowth of the lymphangioma and improve the patient's neurological dysfunctions, which included seizures and cognitive deterioration. After administration of everolimus, the size of the

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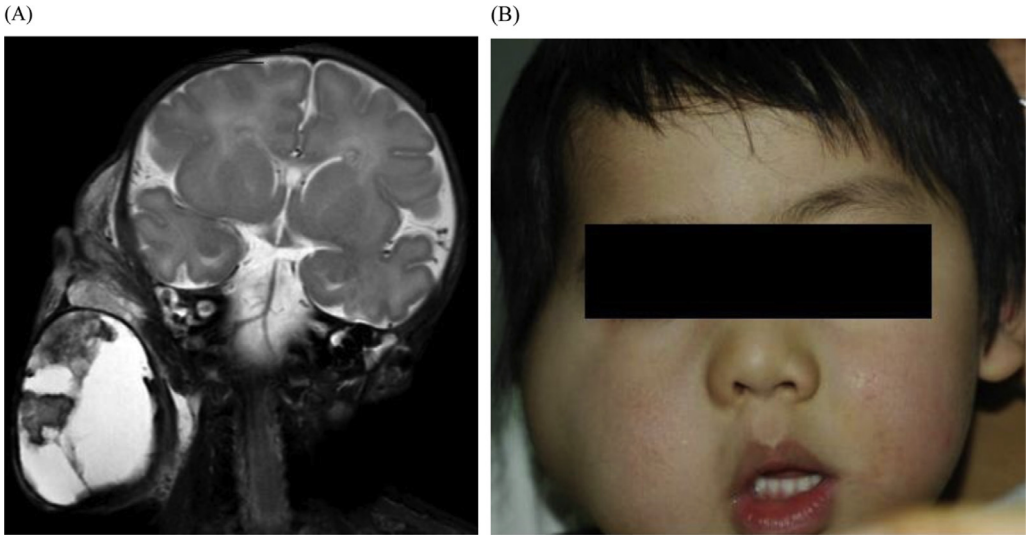

FIGURE 1. (A) Neck magnetic resonance image, obtained on the day after birth, depicts an approximately 11 cm, multiseptated cystic mass with hemorrhage on the right neck involving the parotid, carotid, submandibular, and submental spaces and the supraclavicular fossa, suggestive of cystic lymphangioma. (B) The patient exhibited a markedly large regrown cystic lymphangioma on his right anterolateral neck. The color version of this figure is available in the online edition.

lymphangioma increased but at a slower rate without need of further surgical resection. His seizures were also well controlled, and the parents reported improvement in the patient's alertness. We did not observe remarkable adverse effects related to everolimus, excluding several episodes of mild stomatitis.

On presumptive diagnosis of PROS in patients with overgrown tissues or organ issues, clinicians are required to record a detailed clinical evaluation and perform careful physical examination, especially cardiovascular evaluation and baseline imaging studies, in addition to genetic confirmation and proper genetic counseling. Other comorbidities, such as seizures, intellectual disability, behavioral problems, or speech and motor dysfunction, are examined, as well as heart, kidney, swallowing, or orthopedic problems are considered through a multidisciplinary perspective. Regarding

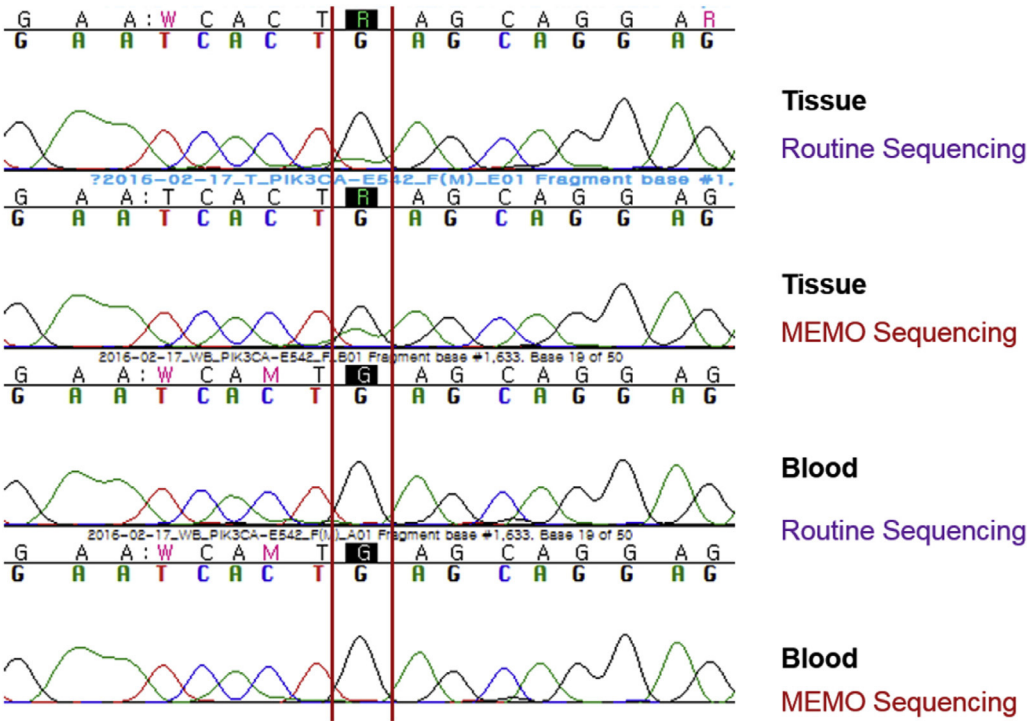

FIGURE 2. Demonstration of the *PIK3CA* c.1624G>A somatic mosaic mutation in the patient's tissue and blood using mutant enrichment with 3′-modified oligonucleotides (MEMO) sequencing. The color version of this figure is available in the online edition.

treatment, mTOR inhibitors could be a viable option for favorable prognosis and improved clinical outcome.

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