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Exudative Retinal Astrocytic Hamartomas and Papilledema in a Patient with Tuberous Sclerosis Complex and Subependymal Giant Cell Astrocytoma: A Case Report

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Dear Editor,

Tuberous sclerosis complex (TSC) is a multisystem disease characterized by hamartomatous growth that commonly affects the brain, skin, kidneys, eyes, and heart. Incidence of TSC is estimated to be 1 in 6,000 [1]. About half of patients with TSC have retinal astrocytic hamartomas (RAH), which are the most common ocular manifestations of TSC. RAH are usually asymptomatic and stationary lesions, while some RAH do enlarge causing complications like cystoid macular edema, retinal detachment, vitreous hemorrhage, or neovascular glaucoma [1–3]. Brain lesions of TSC include cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas (SEGA). SEGA are found in 5% to 14% of TSC patients [1]. This is the first report for exudative RAH accompanied with severe papilledema controlled by anti–vascular endothelial growth factor (anti-VEGF) treatments in a Korean TSC patient with SEGA. Written informed consent for publication of the research details and clinical images was obtained from the patient.

A 21-year-old man with known TSC presented for progressive visual loss in both eyes over 3 to 4 months. He had a medical history of facial angiofibromas, epilepsy with findings of multiple cortical tubers on vigabatrin, attention deficit, aggressiveness, developmental delay, and renal angiomyolipomas (Fig. 1A–1D). He also had SEGA in the right lateral ventricle with resultant severe obstructive hydrocephalus and papilledema (Fig. 1B, 1C). However, he did not complain of a headache, which was thought to be because he had been on anticonvulsants (lacosamide 100 mg and levetiracetam 500 mg) for more than 10 years. His visual acuity was light perception in each eye. Anterior segment exam was not remarkable, including no neovascularization on the iris. In both eyes, there were extensive optic disc swellings with peripapillary exudates and hemorrhages, marked retinal vascular tortuosity, and macular exudates (Fig. 1E, 1F). Optical coherence tomography of both eyes revealed severe disc swellings, subretinal fluid, multiple hyper-refractive foci in the inner retina and above the retinal pigment epithelium due to exudates, and destructive outer retina, not available to measure the thickness (Fig. 1G, 1H). Fluorescein angiogram showed severe staining and leakage in both optic discs and peripapillary vessels, and hypo-blockages from hemorrhages and plaque lesions of RAH (Fig. 1I–1L). He got intravitreal injections of anti-VEGF (bevacizumab, 1.25 mg in 0.05 mL) in both eyes with 2-week intervals. The peripapillary swelling and fluid improved after each injection, facilitating the plaque lesions of RAH visible; however, his visual acuity eventually dropped to no light perception in both eyes (Fig. 1M–1P). A month after the second injection, he was planned to undergo a partial removal for SEGA. However, he refused further treatment and moved to a nursing facility, leading

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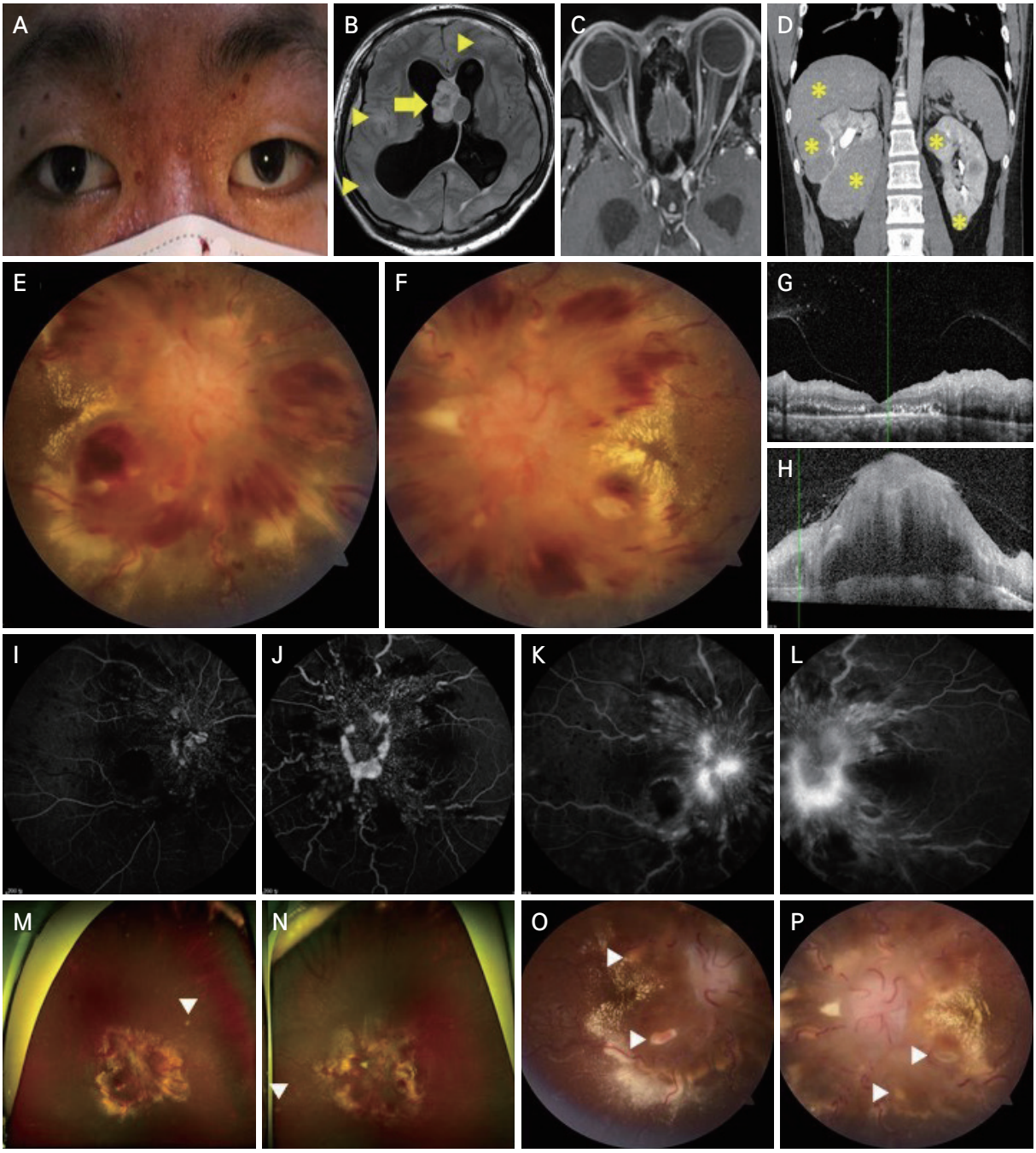

Fig. 1. Clinical images of exudative retinal astrocytic hamartomas (RAH) and severe papilledema in a patient with tuberous sclerosis complex, treated with intravitreal injection of anti–vascular endothelial growth factor (anti-VEGF). (A) Frontal photograph showing multiple facial angiofibromas. (B,C) Magnetic resonance imaging of the brain. (B) Multiple cortical tubers (arrowheads) and 3.3 × 2.0 cm of the subependymal giant cell astrocytoma in right lateral ventricle (arrow) with hydrocephalus are shown. (C) Bulging both optic discs and increased fluid surrounding both optic nerves, suggesting severe papilledema. (D) Computed tomography of the kidney showing multiple angiomyolipomas (asterisks). (E,F) Fundus photographs showing severe disc swelling with extensive hemorrhages and vessel tortuosity, and macular exduates at the initial presentation. (G,H) Optical coherence tomography images. (G) Hyper-refractivity in the inner retina, suggesting vasculitis, some subretinal fluid, and hyper-refractive foci in the outer retina due to exudates are shown. (H) Peripapillary subretinal fluid is seen. (I–L) Fluorescein angiogram showing extensive staining and late leaking in the optic discs and hypo-blocks around optic disc due to hemorrhages and RAH lesions. (M,N) Two weeks after the first anti-VEGF injection, mild improvement of disc swelling and visible RAH lesions (arrowhead). (O,P) A month after the second anti-VEGF injection, the disc swelling and hemorrhages were improved. There are a few flat lesions of RAH (arrow heads). Written informed consent for publication of the clinical images was obtained from the patient.

to loss of follow-up.

The flat smooth translucent RAH is the most common type of RAH associated with TSC as seen in our patient, occurring in 70% of patients with RAH, which is located in the posterior pole and superficial to retinal vessels. Rarely vitreous hemorrhage may complicate the lesions, presumably due to abnormal vessels involving RAH [1–3]. RAH farther from the disc tend to be stationary, while lesions near the optic disc tend to grow [3]. In our patient, the juxtapapillary RAH could be activated in the setting of severe papilledema secondary to SEGA. *TSC1* or *TSC2* mutations result in the accumulation of hypoxia inducible factor-1α (*HIF-1α*) and increased expression of *HIF*-responsive genes including VEGF [4]. VEGF has been shown to be an important angiogenic factor in malignant astrocytomas of the brain, and it has also been detected in RAH [4]. The hypothesized mechanism for the effect of anti-VEGF agents is the limitation of tumor growth and decreased leakage from the rich vascular network that characterizes RAH lesions [4,5]. In our patient, intravitreal injections of anti-VEGF led to tomographic improvement, while his visual acuities dropped to no light perception, consistent with previous case reports [4,5]. The poor functional response can be attributed to other destructive retinal lesions. However, this case suggests that VEGF antagonism can change the morphology of the more aggressive RAH in the setting of papilledema in a patient of TSC with SEGA.

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