Subthreshold micropulse laser photocoagulation therapy in a case of bilateral retinal astrocytic hamartomas with tuberous sclerosis complex
A case report
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Abstract
Rationale: Report a case of bilateral multiple retinal hamartomas (RAHs) in a patient with tuberous sclerosis complex (TSC) and introduce a new method (subthreshold micropulse laser photocoagulation) for the treatment of RAHs.

Patient concerns: A 20-year-old man with TSC complained of decreased vision and metamorphopsia in both eyes for 2 months. At presentation, visual acuity (VA) was 20/32 in the right eye and 20/40 in the left eye. Fundus photographs, optical coherence tomography, fundus fluorescein angiography (FFA), and indocyanine green angiography indicated multiple RAHs in both eyes.

Diagnoses: Bilateral retinal astrocytic hamartomas.

Interventions: In the right eye, 577 nm photocoagulation was adopted to treat the RAHs with obvious fluorescein leakage in FFA. The paramacular RAHs were treated by subthreshold micropulse mode to minimize the damage to macula. Photocoagulation therapy was administrated in the left eye after 1 dose of intravitreal ranibizumab treatment.

Outcomes: After photocoagulation therapy (including subthreshold micropulse laser photocoagulation for the paramacular RAHs in both eyes), the VA improved to 20/25 OD and 20/32 OS with no recurrence of exudation.

Lessons: About 577 nm photocoagulation for the peripheral RAHs in combination with subthreshold micropulse laser photocoagulation for RAHs in the macular zone is a good option for multiple RAHs in patients with TSC.

Abbreviations: BCVA = best-corrected visual acuity, FA = fluorescein angiography, FFA = fundus fluorescein angiography, OCT = optical coherence tomography, RAHs = retinal hamartomas, SMLP = subthreshold micropulse laser photocoagulation, TSC = tuberous sclerosis complex.

Keywords: micropulse, photocoagulation, retinal hamartomas, tuberous sclerosis complex

1. Introduction
Tuberous sclerosis complex (TSC) is a systemic genetic disorder characterized by hamartomas in multiple organs. Recent epidemiologic studies show that the incidence of TSC is 1/6000 to 1/10,000 live births.\textsuperscript{1,2} Major clinical features of TSC include facial angiofibromas, hypomelanotic macules, retinal hamartomas (RAHs), subependymal giant cell astrocytoma, cardiac rhabdomyomas, and renal angiomyolipomas.\textsuperscript{3} These lesions are mainly caused by mutations of TSC1 and TSC2 genes that encode tumor growth suppressors hamartin (TSC1) and tuberin (TSC2).\textsuperscript{4,5} Approximately 75% to 80% patients with TSC are caused by TSC2 mutations, while TSC1 mutations are less common than TSC1, with the prevalence rate of 10% to 30%.\textsuperscript{6}

Retinal astrocytic hamartoma (RAH) is the most common ophthalmic manifestations in patients with TSC. Reportedly, RAHs occur in 30% to 50% patients with TSC.\textsuperscript{3,7} According to fundus manifestation, RAHs can be classified into 3 types.\textsuperscript{8,9} Type I lesions usually occur as flat, circular, semitransparent, white-gray pattern, and are confined in the retinal nerve fiber layer; type II lesions are prominent, nodular, mulberry-like masses with multiple calcified spots; type III lesions contain the features of both types I and II. Although most RAHs are stationary and do not cause vision impairment, rare cases may develop macular edema, subretinal exudation, exudative retinal detachment, neovascularization, and vitreous hemorrhage.\textsuperscript{10}

By far, there is no standard treatment for RAHs in patients with TSC. Conventional photocoagulation\textsuperscript{11,12} photodynamic therapy,\textsuperscript{13} intravitreal anti-vascular endothelial growth factor (anti-VEGF),\textsuperscript{14,15} vitrectomy surgery,\textsuperscript{16} and systemic mTOR inhibitor\textsuperscript{17} are alternative treatment options for aggressive
RAHs and associated subretinal exudation and neovascularization. However, these treatments are ineffective in many patients and associated with various complications. Here we report a case of TSC with bilateral multiple RAHs and introduce a novel approach of subthreshold micropulse laser photocoagulation (SMLP) therapy in the treatment of RAHs.

2. Case Presentation

A 20-year-old male patient presented to Beijing Tongren Hospital for decreased vision and metamorphosis in both eyes (OU) for 2 months. As the history, he was diagnosed with TSC at the age of 15 and was on regular oral sirolimus (rapamycin) therapy for 5 years. At the initial ophthalmic examination, the best-corrected visual acuity (BCVA) was 20/32 in his right eye (OD) and 20/40 in his left eye (OS). Intracocular pressure was 13 mm Hg in both eyes. According to fundus manifestation, the lesions could be classified into 3 types (Fig. 1A, B). Most of the lesions OD were flat, grayish, translucent, and without calcification, while a lesion in the superiortemporal quadrant had a mulberry-like appearance and demonstrated obvious calcification. Otherwise, the lesions OS consist of multiple calcified spots surrounded by white-gray translucent rings. Ocular B-scan ultrasonography showed a hyperechoic solid mass with calcific foci inferior to the optic nerve in the left eye (Fig. 1C, D). Fundus autofluorescence (FAF) demonstrated patches of hyperautofluorescence corresponding to the lesions on fundus photography (Fig. 1E, F). On optical coherence tomography (OCT), the lesion along the inferotemporal vascular arcade in the right eye showed a hyperreflective dome-shaped mass confined to the retinal nerve fiber layer (Fig. 2A, B). In the left eye, the lesion inferior to the macula demonstrated uneven elevated retinal nerve fiber layer and a large hyporeflective cavity with high reflectivity dots (Fig. 2C, D). Fundus fluorescein angiography (FFA) showed multifocal hyperfluorescence with leakage of fluorescein from the abnormal tumor vessels and dilated retinal capillaries (Fig. 2E-H). The lesions showed hypoautofluorescence throughout the simultaneous indocyanine green angiography (Fig. 2I, J). According to the clinical and image manifestations, the diagnosis of bilateral RAHs was made.

Detailed past medical histories and physical examinations were obtained. The patient developed complex partial seizure at 15 and was diagnosed with TSC based on typical multisystem involvement. Dermatologic examination showed multiple facial angiofibromas on his nose and cheeks in a butterfly distribution (Fig. 3A). Abdominal computed tomography (CT) scan revealed bilateral multifocal renal hamartomas (Fig. 3B). Cranial CT and magnetic resonance imaging (MRI) showed typical lesions including intracranial subependymal calcified nodules (Fig. 3C, D). Psychologic assessment revealed that the patient had autism and mild intellectual disability, which were spectrums of TSC-a associated neuropsychiatric disorders. Oral sirolimus (rapamycin) was administered at an initial daily dose of 2 mg immediately after the diagnosis of TSC. The serum drug concentration, blood cell counts, kidney, and liver functions were monitored. Because of the serum drug concentration was between 15 and 25 ng/mL, the dose was reduced to 1 mg daily and the sirolimus was titrated to serum through concentration of 5 to 10 ng/mL. Despite adequate dosage and duration of sirolimus treatment, one of the renal hamartomas still enlarged rapidly and subsequently oppressed the upper pole and calyx of the right kidney. Thus, the patient underwent partial nephrectomy at 16. Postoperative pathologic examination suggested kidney angiomyolipoma. According to the 2012 International Tuberous Sclerosis Complex Diagnostic Criteria, clinical features of TSC are a principal means of diagnosis; in addition, a pathogenic mutation in TSC1 or TSC2 is can be an independent diagnostic criterion. So in the current visit, gene analysis was performed for the patient and his parents. We detected a mutation of TSC2 gene in the propositus as follows: c.1513C>T; p.Arg505Ter; Het. However, no mutations were detected in his parents.

After discussing the benefits and potential complications of retinal photocoagulation and intravitreal anti-VEGF therapy, written informed consent was obtained from the patient. In the right eye, 577 nm yellow laser with a 200-μm spot diameter and 0.2 seconds duration was applied according to the fundus photography and FFA. RAHs that showed obvious fluorescence leakage were surrounded by laser spots. For RAHs close to the macula, SMLP was adopted to effectively control the RAH progression as well as protect the macula from photomaging. The laser power was determined by the visible laser scar of a trial photocoagulation created with continuous-wave mode for 0.2 seconds with a diameter of 100 μm outside the vascular arcade. In the left eye, intravitreal injection of 0.5 mg ranibizumab was administered to reduce leakage and exudation caused by the RAH inferior to the macula, which was advantageous for further photocoagulation treatment.

Six months after treatment, his VA improved to 20/25 OD. However, the BCVA OS decreased slightly from 20/40 to 20/50. Fundus photography OD showed that the RAHs were surrounded by phocoagulation spots. The number of RAHs remained stable, and there were no subretinal exudation, hemorrhage, and macular edema in the right eye (Fig. 4A, C). However, the paramacular RAH in the left eye slightly enlarged (Fig. 4B). OCT showed an increased macular thickness, enlarged intraretinal optically empty space and posterior shadowing (Fig. 4D). FFA revealed obvious fluorescein leakage from the paramacular RAH (Fig. 4E, F). Therefore, photocoagulation was performed OS. The lesion inferior to the macula was treated by SMLP, and all the lesions that showed leakage in FFA were surrounded by 577 nm laser spots (Fig. 4G). One month later, the VA was stable in the right eye and the BCVA of the left eye increased to 20/32. The patient was followed up in the following 3 months with no recurrence of exudation and the final BCVA was 20/25 OD and 20/32 OS.

3. Discussion

The TSC is an autosomal dominant disorder that results from pathogenic mutation in TSC1 or TSC2 tumor suppressor gene.[5] According to the latest diagnostic criteria, pathogenic mutation in TSC1 or TSC2 is an independent diagnostic criterion of TSC.[3] Previous studies indicate that TSC2 mutations generally produce a more severe phenotype than TSC1 mutations, and TSC2 mutations correlate with a higher rate of ophthalmologic findings than TSC1 mutations.[6-18]

The RAH is present in 30% to 50% of patients with TSC and is one of the major diagnostic criteria of TSC.[3] Typically, RAH is detected with fundoscopy, and the fundus manifestation is the most important diagnosis basis. OCT and FFA are useful in the detection of early stage RAH, and can help identify RAH from other retinal diseases such as retinoblastoma, sarcoidosis, tuberculous choroiditis, optic disc drusen, etc. The typical
Figure 1. (A, B) Wide-angle funduscopic photograph of the right eye (A) and the left eye (B) showed bilateral multiple retinal astrocytic hamartomas (RAHs). The RAHs could be classified into 3 types. Type I RAH was flat, circular and semitransparent without calcification (black arrow). Type II RAH was prominent and nodular with punctate calcification (white arrow). Type III RAH contained the features of both type I and II (red arrow). (C, D) B-scan ultrasonography of the right eye (C) and the left eye (D) showed a hyperechoic solid mass with calcific foci in the left eye. The lesion measured nearly 1.2 mm x 2.7 mm. (E, F) Fundus autofluorescence photograph demonstrated patches of hyperautofluorescence corresponding to the lesions on fundus photography.
Figure 2. (A, B) Optical coherence tomography (OCT) of the right eye showed a type I retinal astrocytic hamartoma (RAH) with abnormal thickening of the nerve fiber layer (NFL) near the inferotemporal vascular arcade. (C, D) OCT of the left eye demonstrated uneven elevated retinal nerve fiber layer and a larger hyporeflective cavity with high reflectivity dots. (E–H) Fundus fluorescein angiography showed multifocal fluorescein leakage in both eyes. (I, J) The RAHs showed hypofluorescence throughout the simultaneous indocyanine green angiography.
characteristics of RAH in fundus photography are bilateral multiple grayish yellow nodules with or without calcification.[6] OCT characteristic features of the RAHs are abnormal thickening of the retinal nerve fiber layer, moth-eaten optically empty spaces, areas of dot-like high and low reflectivity, subretinal exudation, disorganization of the inner layer retina, retinal pigment epithelium layer, etc.[8,19,20] Previous studies found that type I RAH was the predominant type in children and type III was the predominant type in adult.[8,19] In this case, both calcified and noncalcified RAHs are present with type I predominate OD and type III OS. Progression of RAH from none calcified type I to calcified types II and III with age, may explain the fundus feature of this patient.

Most of the RAHs are within retinal nerve fiber layer and do not cause vision problems for a long time. However, in a few cases, RAHs may progress and cause macular edema, exudative retinal detachment, neovascularization, and vitreous hemorrhage.[10,14] For most patients, systemic lesions (including RAHs) are stable under adequate mTOR inhibitor treatment. However, in this case, systemic mTOR inhibitor was adopted with adequate dosage and duration, and the serum sirolimus concentration was maintained between 5 and 10 ng/mL, the RAHs still progress gradually. Therefore, active interventions for the RAHs were necessary to prevent further damage. The BCVA OD was stable after photocoagulation treatment, while the BCVA OS decreased slightly after intravitreal anti-VEGF injection. Given the prominent exudation caused by the paramacular RAH in the left eye, we decided to try to arrest leakage with micropulse photocoagulation.

Conventional lasers, such as krypton red, argon green and argon yellow laser have been used in the treatment of RAHs.[11,21] Nevertheless, conventional laser photocoagulation occasionally causes undesirable adverse effect. The most common side effect is the thermal destruction of neurosensory retina which leads to subsequent vision impairment. Besides, conventional photocoagulation in the macular zone can induce choroidal neovascularization. The SMLP is a novel treatment for macular disorders such as diabetic macular edema and central serous chorioretinopathy.[22] The diffusion of heat to surrounding tissues is minimized in SMLP, thus scarring is prevented. In this case, we use 577 nm yellow laser for SMLP because xanthophyll (the pigment located in the inner and outer plexiform layers of the macula) absorbs the yellow light only minimally. So yellow light is relatively safe when applied near the fovea. To the best of our knowledge, this is the first report of TSC-associated RAHs that were successfully treated with 577 nm SMLP. Considering the different types and severity of RAHs, it is unknown whether SMLP therapy is effective in other cases. Therefore, studies with more patients and longer follow-up period are needed.
Figure 4. (A, C) Funduscopic photograph and optical coherence tomography (OCT) of the right eye at 6-month follow-up showed that the retinal astrocytic hamartoma (RAH) remained stable after photocoagulation treatment. (B, D) Funduscopic photograph and OCT of the left eye after intravitreal ranibizumab treatment showed that the paramacular RAH enlarged with increased exudation. (E, F) Fundus fluorescein angiography (FFA) of the left eye showed obvious hyperfluorescence and late-phase leakage from the RAH inferior to the macula. (G) Funduscopic photograph after photocoagulation treatment in the left eye.
4. Conclusion
The RAH occurs in nearly half of the patients with TSC. The finding of multiple RAHs is determined to be significant and specific enough as a major feature in the diagnosis of TSC. Although most RAHs in patients with TSC are stable throughout lifetime, in some rare cases, aggressive RAHs can lead to extensive exudation, neovascularization, and retinal detachment. RAHs that show obvious leakage in FFA and significant uplift in OCT should be treated timely and properly. Photocoagulation is an effective treatment for aggressive RAHs. About 577 nm subthreshold micropulse laser photocoagulation could be a novel treatment alternative for RAHs close to the macula.

Acknowledgment
The authors thank Professor Zhang Hongbing for careful reviewing the draft of this manuscript and making constructive recommendations.

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References
[1] Osborne JP, Jones AC, Burley MW, et al. Non-penetrance in tuberous sclerosis. Lancet 2000;355:1698.
[2] O’Callaghan FJ, Shiel AW, Osborne JP, et al. Prevalence of tuberous sclerosis estimated by capture-recapture analysis. Lancet 1998;351:1490.
[3] Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 international tuberous sclerosis complex consensus conference. Pediatr Neurol 2013;49:243–54.
[4] European Chromosome 16 Tuberous Sclerosis Consortium. Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell 1993;75:1303–15.
[5] van Slegtenhorst M, de Hooft R, Hermans C, et al. Identification of the tuberous sclerosis gene tsc1 on chromosome 9q34. Science 1997;277:805–8.
[6] Hodgson N, Kinori M, Goldbaum MH, et al. Ophthalmic manifestations of tuberous sclerosis: a review. Clin Exp Ophthalmol 2017;45:81–6.
[7] Aronow ME, Nakagawa JA, Gupta A, et al. Tuberous sclerosis complex: Genotype/phenotype correlation of retinal findings. Ophthalmology 2012;119:1917–23.
[8] Bai DY, Wang X, Zhao JY, et al. Comparison of color fundus photography, infrared fundus photography, and optical coherence tomography in detecting retinal hamartoma in patients with tuberous sclerosis complex. Chin Med J (Engl) 2016;129:1229–35.
[9] Zimmer-Galler IE, Robertson DM. Long-term observation of retinal lesions in tuberous sclerosis. Am J Ophthalmol 1993;119:318–24.
[10] Mennel S, Meyer CH, Peter S, et al. Current treatment modalities for exudative retinal hamartomas secondary to tuberous sclerosis: review of the literature. Acta Ophthalmol Scand 2007;85:127–32.
[11] Vrabec TR, Augsburger JJ. Exudative retinal detachment due to small noncalcified retinal astrocytic hamartoma. Am J Ophthalmol 2003;136:932–4.
[12] Khawly JA, Matthews JD, Machemer R. Appearance and rapid growth of retinal tumor (reactive astrocytic hyperplasia?). Graefes Arch Clin Exp Ophthalmol 1999;237:78–81.
[13] Eskelin S, Tommila P, Paloszari T, et al. Photodynamic therapy with verteporfin to induce regression of aggressive retinal astrocytomas. Acta Ophthalmol 2008;86:794–9.
[14] Saito W, Kase S, Ohgami K, et al. Intravitreal anti-vascular endothelial growth factor therapy with bevacizumab for tuberous sclerosis with macular oedema. Acta Ophthalmol 2010;88:377–80.
[15] Nakayama M, Keino H, Hirakata A, et al. Exudative retinal astrocytic hamartoma diagnosed and treated with pars plana vitrectomy and intravitreal bevacizumab. Eye (Lond) 2012;26:1272–3.
[16] Vilaplana D, Castilla M, Poposki V, et al. Acquired retinal astrocytoma managed with endoresection. Retina 2006;26:1081–2.
[17] Zhang ZQ, Shen C, Long Q, et al. Sirolimus for retinal astrocytic hamartoma associated with tuberous sclerosis complex. Ophthalmology 2013;122:1947–9.
[18] Dubois SL, Jorvik S, Franza DN, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of tsc2, compared with tsc1, disease in multiple organs. Am J Hum Genet 2001;68:64–80.
[19] Shield CL, Benevides R, Materin MA, et al. Optical coherence tomography of retinal astrocytic hamartoma in 15 cases. Ophthalmology 2006;113:1553–7.
[20] Shields CL, Say EAT, Fuller T, et al. Retinal astrocytic hamartoma arises in nerve fiber layer and shows “moth-eaten” optically empty spaces on optical coherence tomography. Ophthalmology 2016;123:1809–16.
[21] Bloom SM, Mahi CF. Photocoagulation for serous detachment of the macula secondary to retinal astrocytoma. Retina 1991;11:416–22.
[22] Scholz P, Altay L, Fauser S. A review of subthreshold micropulse laser for treatment of macular disorders. Adv Ther 2017;34:1528–35.