Intravitreal anti-vascular endothelial growth factor therapy with bevacizumab for tuberous sclerosis with macular edema

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ABSTRACT.

Purpose: To describe two patients with macular edema secondary to tuberous sclerosis complex (TSC), who were treated with intravitreal bevacizumab injection.

Methods: Interventional case reports. Bevacizumab 1.25 mg was injected into the vitreous of two patients with TSC-associated macular edema/ exudative retinal detachment. VEGF concentration in the vitreous fluid was measured by ELISA in one of these patients.

Results: Case 1. 22-year-old woman with TSC was diagnosed as having multiple retinal hamartomas in both eyes. Eleven years later, the patient developed macular edema with epiretinal membrane formation in the right eye. The patient underwent pars plana vitrectomy with retinal photocoagulation for retinal tumors. VEGF concentration in the vitreous fluid was high compared to that in patients without retinal vascular diseases. Recurrent macular edema was resolved by intravitreal injection of bevacizumab. Case 2. 32-year-old woman with TSC-associated retinal hamartoma, temporally showing macular exudative retinal detachment, developed the neovascularization originated from the tumor. By intravitreal bevacizumab injection, the

tumor size markedly reduced with regression of the neovascularization.

Conclusions: These results suggest that VEGF derived from retinal hamartomas causes macular edema associated with TSC. Intravitreal injections of bevacizumab may be a useful therapeutic option for macular edema secondary to TSC.

Keywords: bevacizumab - exudative retinal detachment - macular edema - retinal hamartomas - tuberous sclerosis - vascular endothelial growth factor

Introduction

Tuberous sclerosis complex (TSC) is a syndrome characterized by hamartomatous growths in multiple organs (Roach et al. 1998). Patients with TSC generally develop retinal astrocytic hamartomas; however clinical symptoms of patients with the retinal hamartomas are generally asymptomatic and most astrocytic hamartomas remains unchanged in size or regress during life (Zimmer-Galler & Robertson 1995). Symptomatic ocular complications rarely represent and include macular edema, exudative retinal detachment (RD), vitreous hemorrhage (VH), and neovascular glaucoma (Mennel et al. 2007). Symptomatic macular edema or exudative RD has previously been reported in only 7 eyes (Mennel et al. 2007). Argon laser photocoagulation or photodynamic therapy against retinal hamartoma may be effective for these complications (Bloom & Mahl 1991; Mennel et al. 2007). However, multiple laser treatment procedures may cause laser-induced choroidal neovascularization (Bloom & Mahl 1991). Thus, the therapeutic strategy for macular edema secondary to TSC, and the pathogenic mechanism are controversial. We report two patients with macular edema/ exudative RD secondary to TSC who underwent intravitreal

bevacizumab injection, from the result of high intravitreal vascular endothelial growth factor (VEGF) levels in one patient.

Case reports

Case 1

In 1995, a 22-year-old woman with TSC was referred for ophthalmologic examination. At 8 years of age, the patient was diagnosed as having TSC based on clinical findings including facial angiofibromas, renal angiomyolipoma, and subependymal nodules.

The patient's visual acuities were 20/15 OU. Funduscopic examination demonstrated scattered slightly elevated gray-white tumors with partially calcification located in the retinal surface OU. Fluorescein angiography (FA) demonstrated early hyperfluorescence with late leakage corresponding to retinal tumors OU. The patient was diagnosed as having retinal hamartoma type 3 associated with TSC.

In 1998, vitreous hemorrhage (VH) occurred OD, but spontaneously resolved within six months. In 2002, visual acuity decreased to 20/ 400 OD. Ophthalmoscopic examination showed posterior subcapsular cataract, cystoid macular edema, fibrovascular membrane formation, and retinochoroidal atrophic lesion located on the

superior side of the macula OD, although left eye remained no changed. Thereafter, the patient discontinued follow-up. In 2004, the patient complained of blurred vision OD, whereas visual acuity remained unchanged. The patient underwent cataract surgery of the right eye, because cataract developed despite disappearance of macular edema. Eight weeks after cataract surgery, the optics of the intraocular lens was completely closed by contraction of the anterior capsule OD. Visual acuity improved to 20/200 after YAG laser capsulotomy for the anterior capsule.

In May 2006, visual acuity decreased to 20/500 OD. Macular edema recurred OD (Fig. 1A) and late-phase FA demonstrated cystoid macular edema and marked leakage from retinal tumors and retinal capillary vessels (Fig. 1B). Optical coherence tomography (OCT) revealed macular edema with epiretinal membrane OD (Fig. 1C). In November 2006, the patient underwent pars plana vitrectomy (PPV) with epiretinal membrane removal and retinal photocoagulation to the retinal tumors. After obtaining informed consent, VEGF concentration in the vitreous fluid collected was measured by ELISA (BioSource International, Camarillo, CA). The concentration was 68.5 pg/ml in this patient, while vitreal VEGF levels in ten patients with macular hole were under

detectable levels.

One month after second surgery, visual acuity improved to 20/ 300. Funduscopy revealed photocoagulation scars corresponding to the tumors and disappearance of macular edema. The dye leakage from retinal capillary vessels in FA decreased (Fig. 2A~C). Five months after PPV, visual acuity decreased to 20/ 500 OD. Macular edema recurred (Fig. 3A), and FA showed increased retinal capillary leakage. Based on the patient's high intravitreal VEGF level, after informed consent following IRB approval, the patient underwent intravitreal injection of bevacizumab 1.25 mg. One week after the injection, macular edema rapidly improved (Fig. 3B) and visual acuity increased to 20/400. Thereafter, macular oedema recurred again; recurrent macular oedema disappeared by performing additional laser photocoagulation for tumours causative of exudation.

Case 2

32-year-old woman presented with central visual loss of the right eye for the last two weeks. The patient was diagnosed as having tuberous sclerosis because she had a

medical history of seizure and pathological diagnosis of subependymal giant cell astrocytoma and facial angiofibromas.

Her visual acuities was 20/30 OD, and 20/15 OS. Anterior segment and lens were clear, OU. Funduscopy revealed macular exudative RD with lipoid exudates and an elevated, oval-shaped whitish retinal tumor without calcification, located in parapapillary area (Fig. 4A). The tumor located on the retinal surface and involved neovascularization on the surface (Fig. 4A, arrow). Late-phase FA revealed marked leakage from the tumor, the neovascularization, and retinal capillary vessels (Fig. 4B). A diagnosis of retinal hamartoma type 1 in association with TSC was made. One month later, exudative RD spontaneously regressed and visual acuity improved to 20/20, OD. However, the neovascularization originated from the tumor remained unchanged. Since we considered that the neovascularization caused VH like case 1, after informed consent, the patient received intravitreal bevacizumab 1.25 mg injection. One week after the injection, the tumor size reduced with regression of the neovascularization (Fig. 5A). The late leakage from the tumor and retinal capillary vessels in FA decreased (Fig. 5B). Three months after the injection, the tumor almost regressed (Fig. 5C) and visual acuity increased of

20/ 16, OD.

Discussion

TSC has been determined to result from mutations in TSC1 (hamartin) and TSC 2 (tuberin) tumor suppressor gene (Cheadle et al 2000). TSC1 and TSC2 proteins are responsible for the regulation of cell growth and tumourigenesis: TSC1/ TSC2 complex controls Ras homologue enriched in brain (Rheb) and subsequently inhibits the mammalian target of rapamycin (mTOR), a key regulator in signaling pathway of cell proliferation and organ size (Schwartz et al 2007). Therefore, mutated TSC1/TSC2 complex causes uncontrolled cell growth and proliferation. Moreover, it is elucidated that hamartomas associated with TSC, involving the other organs (kidney, brain, and skin) except the eyes, are highly angiogenic (Arbiser et al. 2002) and can express angiogenic factors including VEGF (Nguyen-Vu et al. 2001). However, as far as we know, there are no reports which detected expression of VEGF in retinal hamarotmas. Therefore, we hypothesized that retinal hamartomas are also highly angiogenic and express VEGF, which lead to ocular complication including macular edema.

In this study, VEGF concentration in the vitreous fluid taken intraoperatively in case

1 was apparently high, compared to the levels in patients without retinal vascular diseases. Retinal hamartomas in two patients involved VH (case 1) and the neovascularization originated from retinal tumors (case 2), suggesting that retinal hamartomas associated with TSC are well-vascularized tumors and possibly express VEGF. Based on the result of high intravitreal VEGF concentration in case 1, intravitreal bevacizumab injection was tried in two patients with TSC-associated macular edema/ exudative RD. After injection, not only macular edema, VA, OCT, and FA findings rapidly improved (Case 1) but the tumor size and tumor-associated neovascularization were rapidly attenuated (Case 2), although these two patients possibly may have recurrence of macular edema after a long-term follow-up. Therefore, the results in this study strongly suggest that VEGF derived from retinal astrocytic hamartomas plays a potential role in the pathogenesis of macular edema/ exudative RD secondary to TSC. As far as we know, there are no reports demonstrating effectiveness of intravitreal bevacizumab injection in patients with TSC-associated macular edema.

In both patients 1 and 2, macular oedema disappeared rapidly by a single intravitreal bevacizumab injection. However, macular oedema secondary to TSC may be repeated,

such as in patient 1, in a long-term follow-up.When macular oedema recurred, performing intravitreal bevacizumab injection 3-6 times continuously every 4-6 weeks may be considered (Soliman et al. 2008). Moreover, additional retinal photocoagulation or photodynamic therapy for tumours causative of exudation may also be considered after intravitreal bevacizumab injection. When we follow up patients with TSC, to detect initial or recurrent macular oedema in early stage by performing OCT regularly is mandatory for preventing poor visual prognosis (Massin et al. 2006).

In conclusion, intravitreal anti-VEGF antibody injection including bevacizumab might be a therapeutic option for macular edema/ exudative RD secondary to TSC.

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Figure legends

Fig. 1. Fundus photographs of the right eye before pars plana vitrectomy in case 1.

A, Fundus photograph demonstrates scattered slight elevated whitish retinal tumors located on the surface of the retina, with partially calcification (arrow). Macular edema with epiretinal membrane and fibrovascular membrane are also seen. B, Late-phase fluorescein angiography reveals cystoid macular edema and marked leakage from retinal tumors and retinal capillaries. C, Horizontal image of optical coherence tomography through the fovea shows macular edema with epiretinal membrane.

Fig. 2. Fundus photographs of the right eye one month after pars plana vitrectomy in case 1.

A, Fundus photograph demonstrates disappearance of macular edema and retinal photocoagulation scars corresponding to retinal hamartomas. B, Late-phase fluorescein angiography reveals decreased leakage from retinal tumors and retinal capillaries, compared to that of before vitrectomy. C, Optical coherence tomography image shows the disappearance of macular edema.

Fig. 3. Optical cohelence tomography (OCT) findings of the right eye before (A) and one week after (B) intravitreal bevacizumab injection in case 1.

A, OCT image shows the recurrence of macular edema. B, Macular edema markedly reduces.

Fig. 4. Fundus photographs of the right eye at the initial onset in case 2.

A, Fundus photograph shows macular serous retinal detachment with lipoid exudates and an elevated whitish retinal tumor located on infero-nasal side of the optic disc. The tumor complicates neovascularization on the surface (arrow). B, Late-phase fluorescein angiography reveals marked leakage from the tumor, neovascularization (arrow), and retinal capillary vessels.

Fig. 5. Fundus photographs of the right eye one week after (A,B) and three months after (C) intravitreal bevacizumab injection in case 2.

A, The tumor size reduces to less than one-half, with regression of the neovascularization. B, The late leakage from the tumor and retinal capillary vessels in fluorescein angiography decreases. C, The tumor almost regresses.

Figure1

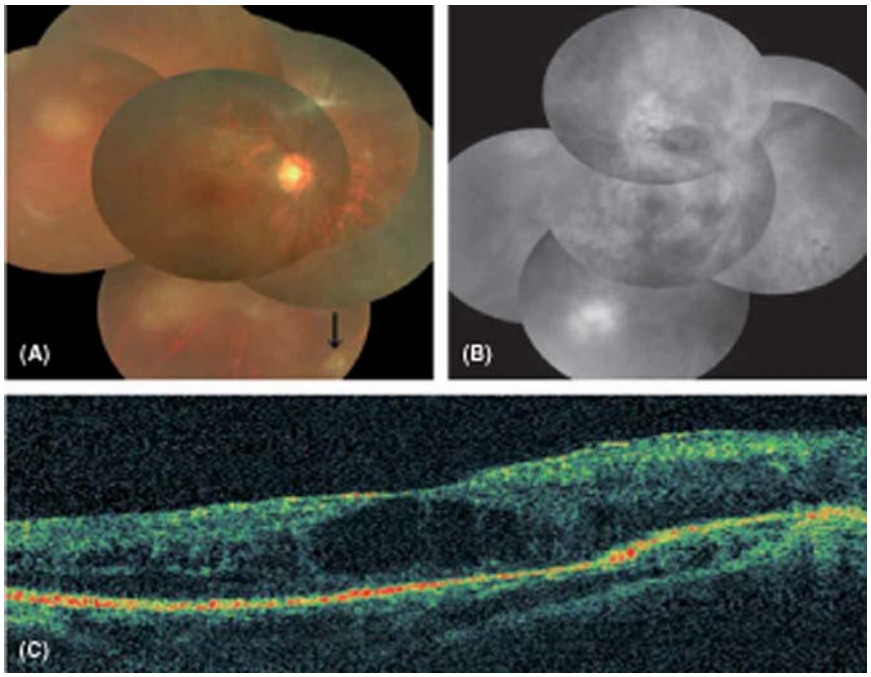
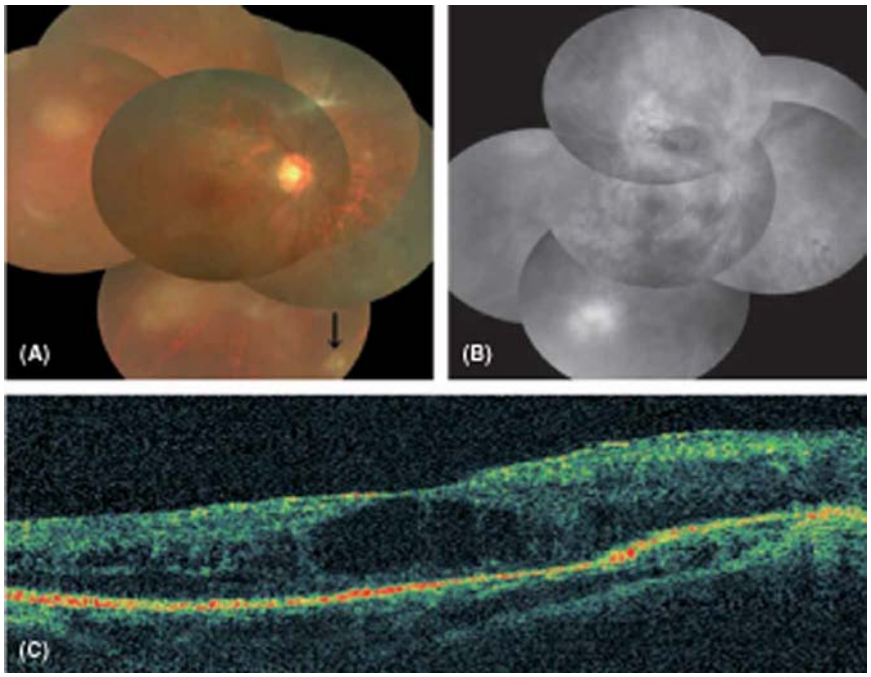


Figure2



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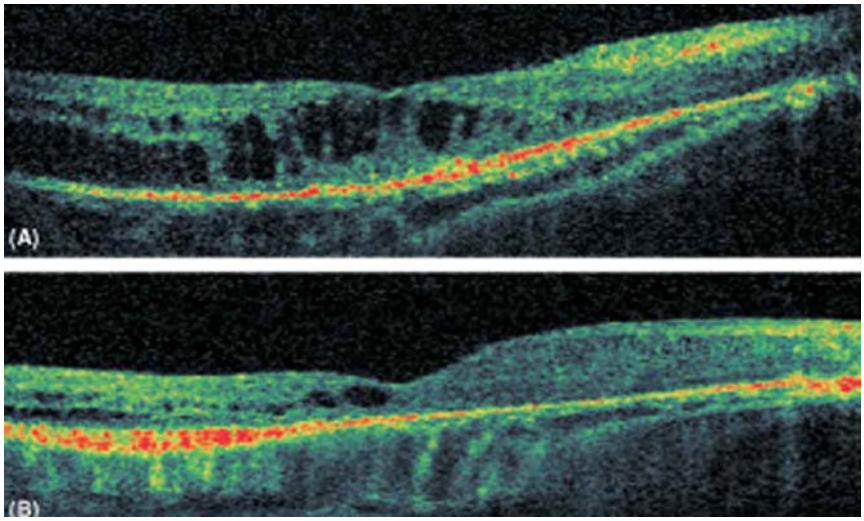

Figure4

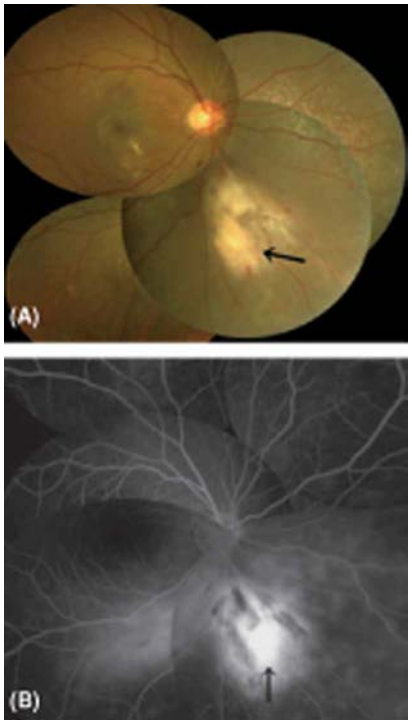

Figure5