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CASE REPORT

Partial thickness sclerectomy and intravitreal anti-VEGF therapy for intractable uveal effusion syndrome

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Abstract

Purpose To report a case series of three patients with intractable uveal effusion syndrome (UES), treated with partial thickness sclerectomy and intravitreal anti-VEGF therapy.

Methods Three patients with intractable UES were included. All patients underwent intravitreal anti-VEGF therapy to facilitate resolution of uveal effusion. The concentrations of IL-1β, IL-6, IL-8, IL-10, IL-12p70, TNF and VEGF in aqueous humor were measured.

Results After the last intravitreal injection, all three eyes had total resolution of the chorioretinal detachment or subretinal fluid. One eye experienced improvement in visual acuity. All patients were free from recurrence during the follow-up period. Aqueous IL-6, IL-8 and VEGF concentrations were elevated in all cases.

Conclusions Our current data provided the evidence that VEGF was increased in eyes with intractable UES and anti-VEGF therapy was effective, suggesting that partial thickness sclerectomy and intravitreal anti-VEGF therapy could be a new choice for intractable UES.

Keywords Intractable uveal effusion syndrome · Intravitreal anti-VEGF therapy · Aqueous VEGF concentration

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Introduction

Uveal effusion syndrome (UES) is an extremely rare disease manifested by suprachoroidal fluid accumulation with serous choroidal and retinal detachment, and is combined with hyperpresbyopia or nanophthalmos in some cases. It is a diagnosis of exclusion that can only be made in the absence of secondary causes of choroidal effusion. Submacular fluid accumulation is common and is often the main cause of vision loss [1, 2]. The probable hypotheses of pathophysiological mechanisms suggest that it may be caused by altered scleral permeability, vortex vein compression or a non-specific choroidal inflammation [1, 3]. For the treatment of UES, the suggested therapy is partial thickness sclerectomy [4]. Nevertheless, due to the recalcitrant nature of the fluid, surgery is frequently

performed to hasten the resolution of swelling and restore vision.

Over the past several decades, vascular endothelial growth factor (VEGF) has become an important pathologic angiogenic factor in several eye diseases, including age-related macular degeneration, diabetic retinopathy and retinal vein occlusion [5, 6]. It has been shown that anti-VEGF antibodies can reduce not only VEGF level, but also inflammation [7]. Therefore, we tried anti-VEGF therapy for the resolution of uveal effusion.

This article presented a case series of three patients with intractable UES, treated with sclerectomy and intravitreal anti-VEGF therapy. We also reported the inflammatory cytokines and VEGF level in the aqueous humor in the cases.

Methods

A retrospective case series of three individuals with intractable UES was conducted. The diagnosis of UES is based on the following criteria proposed by Uyama et al. (1) the fundus showed bullous retinal detachment in the lower periphery without any evidence of retinal break; (2) subretinal fluid was easily shifted according to the head position; (3) fluorescein angiography did not demonstrate any leakage from the choroid into the subretinal space; (4) retinal detachment was accompanied by annular peripheral flat or bullous ciliochoroidal detachment; (5) ora serrata was easily seen without scleral depression; and (6) other causes of ciliochoroidal detachment such as hypotony, intraocular tumor, rhegmatogenous retinal detachment, and intraocular inflammation were excluded. [8] Intractable UES was diagnosed if there was no reduction of fluid in the choroidal effusion 4 weeks after partial thickness sclerectomy, or if the fluid accumulation recurred.

All eyes underwent partial thickness sclerectomy performed using Casswell's technique by the same doctor. Briefly, four rectangular 7 by 8 mm scleral flaps were fashioned centered at the equator in four quadrants, respectively. The entry sites of the vortex veins and their presumed intrascleral course were specifically avoided. The flaps were dissected to an almost full thickness depth, so that the blue color of the choroid was clearly visible. As the sclera flap was resected totally, the thin deep scleral bed became wet with fluid passing out of the choroid [4]. No attempt was made to drain subretinal fluid.

All patients accorded with intractable UES received either 1.25 mg/0.05 mL of bevacizumab or 0.5 mg/0.05 mL of ranibizumab injected intravitreally under standard sterile conditions. The use of the off-label drug and its potential risks and benefits were discussed in detail with all patients, and formal written consent was obtained. Aqueous humor samples were collected before performing intravitreal injection. The concentrations of IL-1β, IL-6, IL-8, IL-10, IL-12p70, TNF and VEGF were measured by applying a cytometric bead array (Nos. 552932, 558336; BD Bioscience, San Jose, CA) with flow cytometry (BD FACSCalibur; BD Bioscience). Based on our previous experience, the level of inflammation cytokines and VEGF in aqueous humor of senile cataract was generally below detectable threshold [9].

Results

Case 1

An 89-year-old male presented to our retina clinic with a 1-month history of blurred vision in his left eye in September 2012. He underwent cataract surgery in the left eye in July 2009. The medical records showed a postoperative shallow anterior chamber at that time. He underwent pars plana vitrectomy for epiretinal membrane in September 2009. In June 2010 and January 2012, two rounds of partial thickness sclerectomies were performed because of the diagnosis of UES with retinal detachment. He had no other specific ocular or medical history, except for a 1-year history of primary hypertension.

At presentation, his best corrected Snellen visual acuity was 6/18 OS, and spherical equivalent was + 0.50 diopter (D) in the left eye. Intraocular pressure (IOP) was normal. Anterior segment examination revealed a well-positioned posterior-chamber IOL. Posterior-segment examination showed inferior retinal detachment with choroidal detachment (Fig. 1a). The scleral thickness and axial length measured by ultrasound were 2.64 and 23.92 mm, respectively. UES recurred. The third surgical dissection was next to impossible due to excess scar tissue. We all knew that he might possibly lose vision due to the recalcitrant fluid, over the 8-month observation time since the

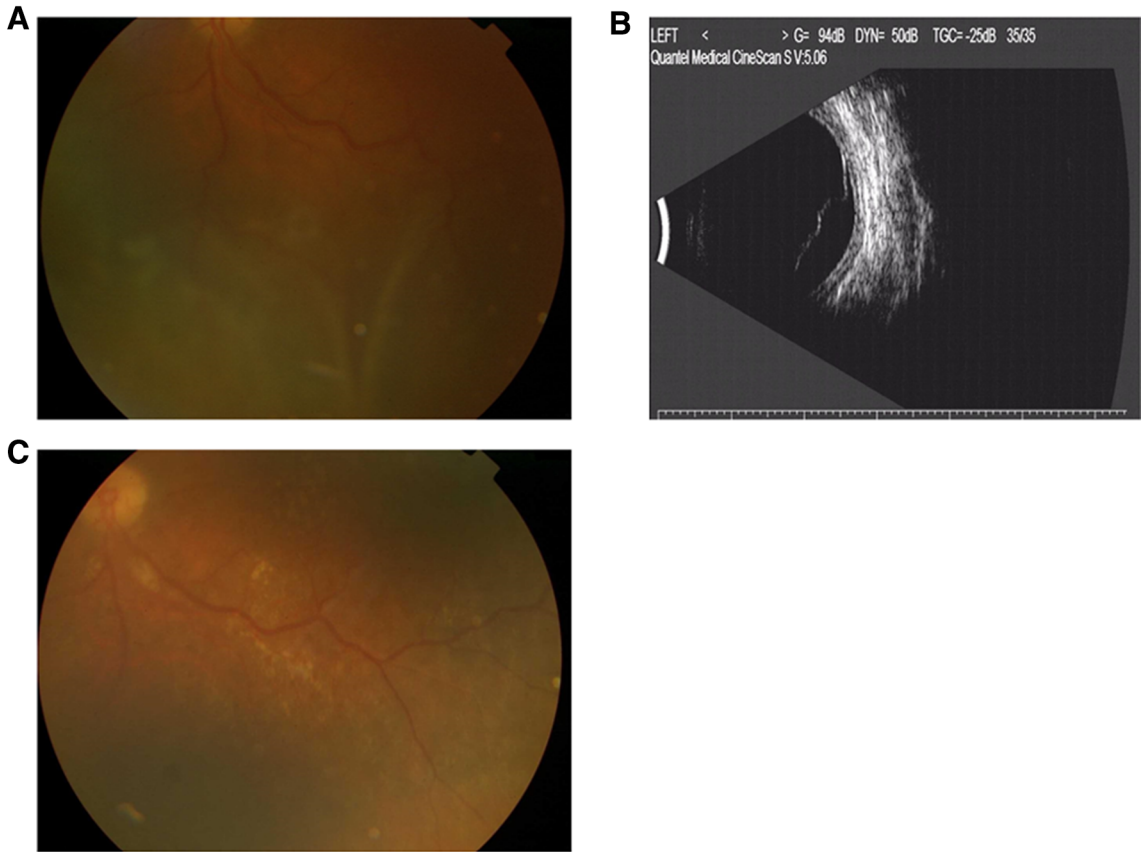

Fig. 1 At presentation, color photograph of the left eye revealed inferior retinal detachment with choroidal detachment (**a**), which was confirmed on ultrasound examination (**b**). At the end of visit, the retina remained completely flat (**c**)

second surgery. Nevertheless, both the patient and the doctor could no longer afford to wait. It was then decided to try anti-VEGF treatment, three times with a ranibizumab injection interval of 4 weeks. Aqueous humor samples were collected before performing intravitreal injection and measured as previously mentioned. The concentrations of IL-8, IL-6 and VEGF were slightly elevated (Table 1). A flat retina was achieved 2 weeks after the first injection. The retina remained flat during the follow-up period (Fig. 1c). However, the BCVA in the left eye was 6/36 over the course of disease.

Case 2

A 55-year-old female was referred to our retina clinic in December 2013 due to decreased visual acuity in the right eye lasting for 3 weeks. She had a history of a retinal detachment in the right eye and received intravitreal injection of 0.4 cc 100% SF_6 in August

Table 1 The concentrations of IL-1β, IL-6, IL-8, IL-10, IL-12p70, TNF and VEGF pre-anti-VEGF injection in aqueous humor of all individuals

Cases	IL-1β (pg/mL)	IL-6 (pg/mL)	IL-8 (pg/mL)	IL-10 (pg/mL)	IL-12p70 (pg/mL)	TNF (pg/mL)	VEGF (pg/mL)
1	< 1.0	39.1	28.3	< 1.0	< 1.0	< 1.0	6.61
2	< 1.0	592.5	15.8	< 1.0	< 1.0	< 1.0	17.3
3	< 1.0	54.8	5.4	< 1.0	< 1.0	< 1.0	20.4

2010. At postoperative 1 week, fundus examination revealed an attached retina in the right eye. Otherwise, she was healthy and had no other medical conditions.

At presentation, her best corrected Snellen visual acuity without any refractive error was 6/36 OD and 3/60 OS. IOP was normal. The anterior segment was normal. Right fundus examination demonstrated inferior retinal detachment involving the macular region, whereas no retinal breaks were found (Fig. 2a). Posterior-segment examination of the left eye revealed retinal pigment and typical 'leopard-spot' changes following resolution of a chronic serous retinal detachment (Fig. 2b). Retinal detachment with choroidal effusion in the right eye was confirmed on ultrasound examination (Fig. 2c). The temporal scleral thickness and axial length in the right eye measured by ultrasound were 1.6 and 22.94 mm, respectively. Fluorescein angiography showed a leopard-spot pattern of granular hyperfluorescence that appeared in the early phase (Fig. 2d). Based on these findings, we diagnosed her with UES.

Partial thickness sclerectomies were performed at four quadrants of the right eye in December 2013. At the follow-up, the subretinal fluid did not resolve at 4 weeks postoperatively. We opted to treat Case 2 empirically with anti-VEGF therapy, twice with a bevacizumab injection interval of 4 weeks. Aqueous humor samples were collected before performing her first intravitreal injection and measured as previously mentioned. The concentrations of IL-8 and VEGF were slightly elevated. The concentration of IL-6 was remarkably elevated (Table 1). One week after the second injection, a flat retina was seen on fundus examination. The retina remained attached during the 10-month follow-up period (Fig. 2e), and an improved

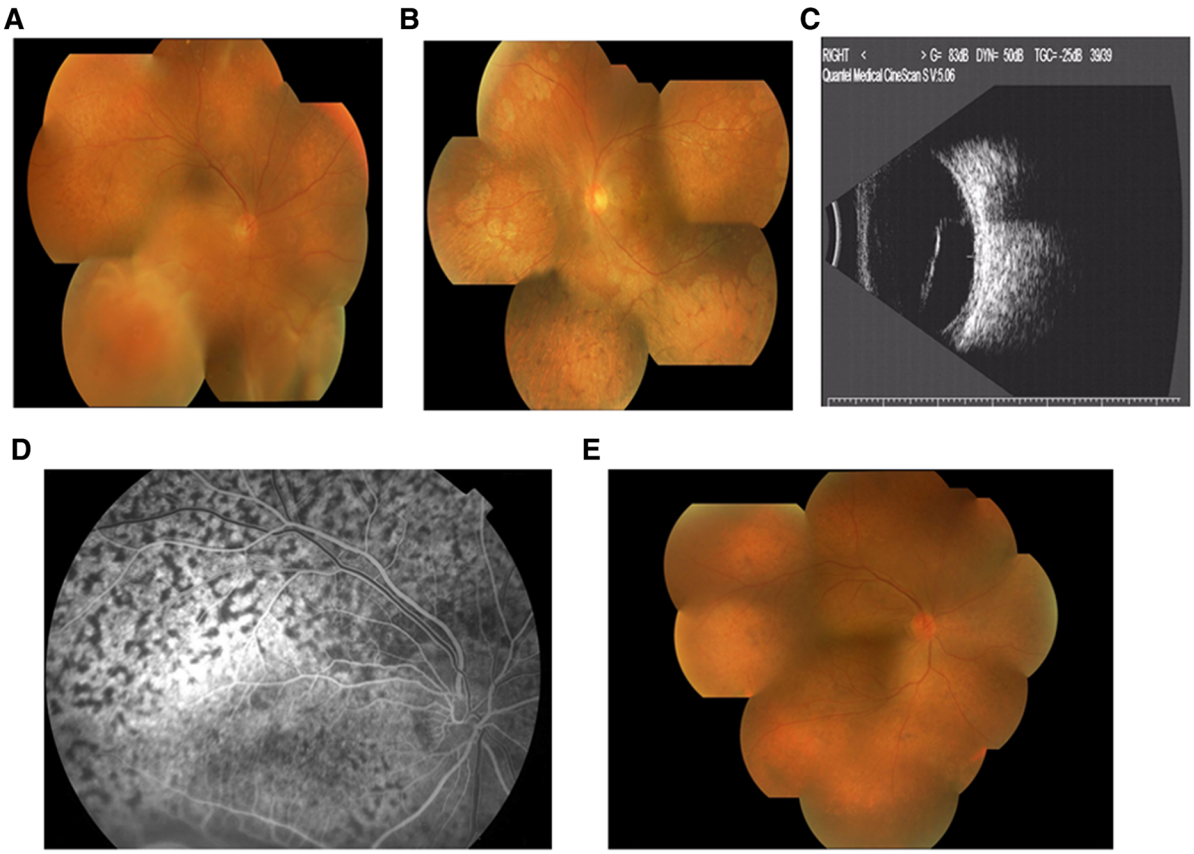

Fig. 2 Fundus photographs of Case 2 on presentation: imaging revealed a inferior serous retinal detachment in the right eye (**a**) and typical 'leopard-spot' changes following resolution of a chronic serous retinal detachment in the left eye (**b**). Ultrasound B-scan showed retinal detachment with choroidal effusion in the right eye (**c**). Fluorescein angiography revealed a leopard-spot pattern of granular hyperfluorescence (**d**). Fundus photograph showed a flat retina 1 week after the second injection (**e**)

best corrected Snellen visual acuity of 6/24 was achieved.

Case 3

A 49-year-old male presented with distorted vision in his left eye that had persisted for 2 weeks in December 2013. He had been wearing glasses for hyperopia since he was younger than 10 years. He had a history of a retinal detachment in the right eye in June 2007 and received eight operations for retinal detachment repair over the next 7 months. Otherwise, he was healthy and had no other medical conditions.

At presentation, his best corrected Snellen visual acuity was 6/24, and spherical equivalent was + 18.0 D in the left eye. IOP was normal. Slip lamp examination showed no specific features, while fundus examination revealed tortuous dilated retinal vessels, serous retinal detachment and subretinal fluid at periphery in the left eye (Fig. 3a). Of note, the temporal scleral thickness and axial length measured by ultrasound were 2.6 and 15.58 mm, respectively. Based on these findings, we diagnosed him as UES with nanophthalmos.

Partial thickness sclerectomies were performed at four quadrants of the right eye in December 2013. The technique used was to fashion a 8 by 5 mm scleral flap at the equator in each quadrant. After the surgery, the subretinal fluid did not resolve at 4 weeks postoperatively. We opted to treat him empirically with anti-VEGF therapy, twice with a bevacizumab injection, with an interval of 8 weeks. Aqueous humor samples were collected before performing his first intravitreal injection and measured as previously mentioned. The concentrations of IL-8, IL-6 and VEGF were slightly elevated (Table 1). Seven weeks after injection (first postoperative visit), fundus examination demonstrated near complete resolution of the choroidal detachment. Repeated injection was given. Four months after the second injection, the retina was found to be completely flat. The retina remained attached at the end of visit (Fig. 3b). However, the best corrected Snellen visual acuity in the left eye remained to be 6/24 over the course of the disease.

Discussion

In this report, we investigated the inflammatory cytokines and VEGF level in the aqueous humor of intractable UES, and the efficacy of anti-VEGF agent in treating UES. To the best of our knowledge, this is the first report regarding intractable UES treated with partial thickness sclerectomy and intravitreal anti-VEGF therapy.

To date, the pathogenesis of UES remains unclear. Based on the scleral outflow hypothesis, surgical management remains the definitive treatment with 83% success after the first operation. The surgical management involving scleral windows and subscleral sclerectomy is proven to be effective in managing UES. Our own previous cases, which included ten eyes of seven patients with idiopathic uveal effusion syndrome from 1999 to 2006, also support this. In

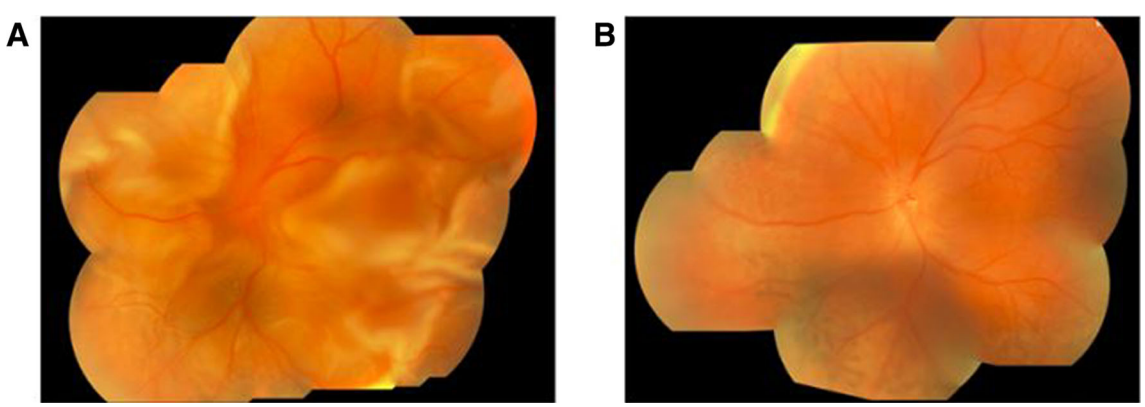

Fig. 3 At presentation, color photograph of the left eye revealed serous retinal detachment and subretinal fluid at periphery (**a**). At the end of visit, the retina remained flat (**b**)

our case series, partial thickness sclerectomy was performed on eight eyes, and partial thickness sclerectomy and vitrectomy were performed on two eyes. The choroid and retina were ultimately reattached in six eyes. However, the disease occasionally takes a relapsing and remitting course after surgery. There are very few reports focused on the failed cases or the intractable UES. Some of the surgeons would try the second, third or even fourth operation according to the previously published case reports [10]. Other less invasive treatment have been studied, including systemic application of glucocorticoid, non-steroid anti-inflammatory drugs, and laser photocoagulation, which all achieved little effect. In our cases, all the three patients of intractable UES had only one functional eye. The visual impairment of their contralateral eye was the consequence of natural course of UES and unsuccessful operative interventions in Case 2 and Case 3, respectively. We treated them with intravitreal anti-VEGF therapy, which might aid in the absorption of subretinal fluid, and further improve visual acuity.

In our cases, IL-6, IL-8 and VEGF concentrations in the aqueous humor were higher in comparison with those control cases with senile cataract [9]. We deduced that IL-6, IL-8 and VEGF might be correlated with the pathogenesis of the intractable subretinal fluid. Our data suggest that VEGF production was increased in eyes with intractable UES and anti-VEGF therapy was effective for the treatment. As to the effect of anti-VEGF treatment on IL-6 and IL-8, experimental studies showed that reducing VEGF decreased the activation state of macrophages [7, 11] and maybe further regulated IL-6 and IL-8 expression. We believe that knowledge of this new treatment may be useful to other surgeons operating on similar eyes. However, further studies are required to investigate the role of IL-6, IL-8 and VEGF in the pathogenesis of intractable UES.

In conclusion, partial thickness sclerectomy and intravitreal anti-VEGF therapy indicated a new choice for intractable UES. The administration of anti-VEGF in cases of intractable UES did not show any adverse outcomes and might probably hasten the resolution of uveal effusion. But since UES is a rare condition, it is unlikely that a clinical trial comparing different treatments is feasible at this time. Further case-series studies are needed to determine the efficacy of anti-VEGF therapy alone.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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