Anti-VEGF Therapy and Retinal Photocoagulation to Prevent Recurrence of Central Retinal Vein Occlusion: Two Case Reports of Young Patients

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Casel: An 18-year-old man. On initial examination, he was diagnosed with central retinal vein occlusion (CRVO) due to optic papillitis. He had no previous systemic and ocular medical history. His best corrected visual acuity was 20/20 for the right eye, but macular edema accompanied by serous retinal detachment was observed about 2 months after the initial examination. Intravitreal anti-VEGF injection was performed, and the symptoms improved. Then, additional photocoagulation was applied to the retinal nonperfusion area, to maintain its normal state.

Case2: A 36-year-old man. He was diagnosed with neovascular glaucoma associated with CRVO in the right eye by his previous physician. Panretinal photocoagulation and intravitreal anti-VEGF injection were performed under maximum-tolerated medical therapy for the right eye. He had diabetes. On initial examination, his visual acuity was 20/100 and his intraocular pressure was 19mmHg. Macular edema and iris neovascularization recurred half a year later, so intravitreal anti-VEGF injection and additional photocoagulation were applied to nonperfusion area. After that, both macular edema and iris neovascularization have settled down. Conclusions: Intravitreal anti-VEGF injection is effective in young patients with CRVO. Also, photocoagulation to nonperfusion area in addition to the continuous treatment with intravitreal anti-VEGF injection seems effective for preventing recurrence.

Key words: central retinal vein occlusion, young patients, anti-VEGF therapy, retinal photocoagulation, preventing recurrence

BACKGROUND

CRVO predominantly occurs in patients over 60 years of age with associated risk factors, such as arteriosclerosis [1], but it is reported for healthy young people under 50 without any etiology [2, 3], with its occurrence at a frequency of 7.5–19.8% [4].

Intravitreal anti-VEGF drug injection for CRVO with macular edema has recently become covered by insurance, which is now adapted to the cases in young people [5–7]. Here, we report some findings in two cases where anti-VEGF antibody was administered for CRVO with macular edema in young people.

CASE PRESENTATION

Case 1

An 18-year-old man was referred to Tokai University Hospital for the retinal hemorrhage of his right eye from two weeks before. The patient had no previous systemic history such as hypertension, diabetes and hyperlipidemia, and ocular medical history. He did not use any medication. On initial examination, his best corrected visual acuity was 20/20 for both eyes, with intraocular pressure of 12 (right) and 15 (left) mmHg, the range of ocular movements was fully bilateral, and there was no relative afferent pupillary defect. Dilated fundus examination of the left eye and both anterior segments was normal. Fundus examination of the right eye revealed severe optic disk edema, superficial retinal hemorrhages in all quadrants, and markedly engorged retinal veins (Fig. 1a and b). Macular edema was not detected by optical coherence tomography (Fig. 2a and b). Goldmann visual field perimetry revealed a slight enlargement of the right blind spot of Mariotte (Fig. 3a and b) but no other obvious abnormality. Since no obvious etiology nor underlying disease was found, CRVO associated with optic disc vasculitis was suspected from the ophthalmological findings at the first visit; thus, 100 mg/d bayaspirin, 150 mg/d kallidinogenase, 90 mg/d carbazochrome sodium sulfonate as well as 3 times/d dorzolamide were prescribed with conservative follow-up observation. Blurred vision in the right eye and the appearance of macular edema were observed two months later (Fig. 4), and subsequent Fluorescein angiography revealed nonperfusion area at the peripheral retina (Fig. 5). He received intravitreal anti-VEGF injection and additional photocoagulation for nonperfusion area, leading to the maintenance of a normal state (Fig. 6).

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Fig. 1 Fundus photograph of the right at the first visit: dilated and meandered retinal veins, flame-shaped/patchy retinal hemorrhages, and redness and swelling of optic papilla are seen (a). No abnormality is found in the left fundus (b).



Fig. 2 Optical coherence tomography at the first visit of case 1 patient: no obvious macular edema is seen in either eye (a and b).



Fig. 3 Goldmann visual field perimetry at the first visit in case 1: enlargement of the right blind spot of Mariotte is seen (a). No abnormality is found in the left eye (b).



Fig. 4 Optical coherence tomography in case 1 after two months: macular edema is seen in the right eye.



Fig. 5 Fluorescein angiography after the treatment in case 1: the area of retinal nonperfusion area at the peripheral retina of the right eye.



Fig. 6 Optical coherence tomography after intravitreal anti-VEGF injection in case 1: macular edema in the right eye has disappeared.





Fig. 7 Fundus photograph and optical coherence tomography for case 2 by the previous doctor at the time of the onset of right CRVO: dilation and meandering of retinal veins in the right fundus, flame-shaped and patchy retinal hemorrhage, soft retinal exudates, and redness and swelling of optic papilla (a) and macular edema (b) are seen.

Case 2

A 36-year-old man was referred to Tokai University Hospital with the diagnosis of neovascular glaucoma associated with CRVO in the right eye. He had been receiving follow-up for diabetes mellitus (HbA1c: 11.1%) including medical treatments and ophthalmology examinations approximately once every three months at a local ophthalmological clinic. Since CRVO developed in the right eye with the complication of macular edema (Fig. 7a and b), he received panretinal photocoagulation and intravitreal anti-VEGF injection with follow-up; however, a complication of neovascular glaucoma was also suspected, so he was introduced to Department of Ophthalmology, Tokai University. On initial examination, his best corrected visual acuity was 20/100 in the right eye and 20/20 in the left eye, with intraocular pressure of 19 (right) and 18 (left) mmHg. Although no clear iris neovascularization was observed in the right anterior segment, CRVO, panretinal photocoagulation spots, and macular edema were found in the fundus (Fig. 8a and b). No abnormality was found in the left eye, including diabetic changes. Because of suspected CRVO with diabetes and neovascular glaucoma, the patient was applied with additional photocoagulation to the gap of coagulation spots in the retina, received gradually reduced prescription by previous physician, and was subjected to follow-up. The intraocular pressure and fundus findings remained in

remission due to the treatment with tafluprost/timolol maleate, brinzolamide, and ripasudil ophthalmic solutions, as well as oral acetazolamide and additional photocoagulation; however, the deterioration of macular edema and iris neovascularization were observed after a half year (Fig. 9a and b), so an additional intravitreal anti-VEGF injection was administered. Since macular edema still remained after that, fluorescein angiography was performed and additional photocoagulation was applied to nonperfusion area (Fig. 10a and b), followed by an additional intravitreal anti-VEGF injection. Currently, both macular edema and intraocular pressure are in good conditions.

DISCUSSION

CRVO is a common disease in the elderly, often in those with the background of systemic diseases such as hyperlipidemia, hypertension, and diabetes [1], but sometimes can occur in healthy young people without any etiology [2, 3]. The patient in the case 1 was an 18-year-old male with CRVO associated with optic papillary edema without obvious etiology or underlying disease. It was unilateral with dilated, tortuous retinal veins and moderate retinal hemorrhage in addition to papillary edema. Based on these conditions, we suspected CRVO caused by optic papillitis as reported by Hayreh [8]. Subtenon injection of triamcinolone acetonide was initially considered because macular edema



Fig. 8 Fundus photograph and optical coherence tomography of the right at the first visit of case 2 patient: spotted hemorrhage/hard white exudate in macula and panretinal photocoagulation spot (a) and macular edema (b) are seen.



Fig. 9 The right anterior segment and optical coherence tomography in case 2 after six months: iris neovascularization (a, white arrowheads) and macular edema (b) are seen.



Fig. 10 Right optical coherence tomography and fluorescein angiography after the first intravitreal anti-VEGF injection in case 2: macular edema remained (a) and the area of retinal nonperfusion area is seen in the arcade vessel (b).

was observed during the course, and the usefulness of steroids for optic papillitis was reported [8]. However, it has been reported that in young people steroid administration to macular edema complicated with retinal vein occlusion raised the incidence rates of glaucoma [9], and that the administration of anti-VEGF antibody drugs was more effective for macular edema complicated with retinal vein occlusion compared with steroid administration or retinal photocoagulation [10]; thus, we chose intravitreal anti-VEGF injection and macular edema was improved successfully. Additional photocoagulation was also applied to nonperfusion area at the peripheral retina that was found by fluorescein angiography performed around the same time, allowing the maintenance of normal condition. The patient in case 2 was a 36-year-old man who had CRVO and macular edema associated with diabetes, and also complicated with neovascular glaucoma. He received intravitreal anti-VEGF injection, resulting in the improvement of macular edema. After that, fluorescein angiography was performed, and photocoagulation was additionally applied to nonperfusion area which was found in the arcade vessel; no recurrence of macular edema has been found. Although anti-VEGF drug is mainly used for the treatment of macular edema, its recurrence and frequent administration associated with the recurrence are yet to be addressed. Intravitreal half-life of anti-VEGF; bevacizumab is only approximately 3 days [11] so that its therapeutic effect is transient, and Kawakami *et al.* reported that the recurrence rate of central retinal vein occlusion without anti-VEGF therapy is reported at a frequency of 64.3% [12].

Matsuyama et al. [13] showed that VEGF levels in the aqueous humor were dramatically reduced by anti-VEGF injection and remained at a low level for up to 8 weeks after anti-VEGF injection when selective retinal photocoagulation to nonperfusion area was used as a combination therapy. In addition, Takamura et al. investigated the involvement of ischemic retina, which is causative of VEGF, in the recurrence of diabetic macular edema after intravitreal administration of bevacizumab, and reported that selective photocoagulation to nonperfusion area after anti-VEGF treatment was effective for maintaining the improved state of edema [14]. In this study, we have been able to maintain the improved state of macular edema by performing selective retinal photocoagulation to nonperfusion area in two young patients, who developed CRVO and received intravitreal anti-VEGF injection. In conclusion, in young patients, intravitreal anti-VEGF injection was effective against macular edema complicated with CRVO. In addition, when macular condition worsens, it seemed effective to reevaluate the retinal circulation by fluorescein angiography and apply additional photocoagulation, in addition to the continuous treatment with anti-VEGF injection, for preventing recurrence.

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