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Case Report *Retina and Uvea*

Managing massive submacular hemorrhage using intravitreal brolucizumab in combination with subretinal tissue plasminogen activator and non-expansile gas – A case report

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ABSTRACT

We report a case of a 60-year-old lady presented to us with a sudden painless diminution of vision in the left eye (LE). Her best-corrected visual acuity (BCVA) was counting fingers close to face in the LE. She was diagnosed with submacular hemorrhage (SMH) secondary to polypoidal choroidal vasculopathy (PCV). We performed a standard 25-gauge pars plana vitrectomy with subretinal tissue plasminogen activator injection along with an intravitreal injection of brolucizumab and perfluoro propane (C3F8) gas injection. Six weeks after the procedure, her BCVA improved to counting fingers at three meters. After another two injections of brolucizumab at one-month intervals, the BCVA improved to 6/9, N6. We present the long-term follow-up of this eye for nearly 18 months with improved visual acuity, that is, 6/36, N24 at the final visit. This technique shows favorable results in the case of massive SMH due to PCV.

Keywords: Intravitreal brolucizumab, Submacular hemorrhage, Subretinal tissue plasminogen activator, Vitrectomized eye

INTRODUCTION

Submacular hemorrhage (SMH) is a common manifestation of choroidal or retinal vascular abnormalities.[1] Cho *et al.* reported that eyes with polypoidal choroidal vasculopathy (PCV) have a three times higher incidence rate of SMH than eyes with neovascular age-related macular degeneration.[2] Massive SMH is a catastrophic complication of PCV with irreversible visual impairment. We report a case of large SMH secondary to PCV, managed with intravitreal injection (IVI) of brolucizumab, along with subretinal tissue plasminogen activator (tPA) through pars plana vitrectomy (PPV) and non-expansile gas injection. To the best of our knowledge, there are no reports about using IVI of brolucizumab in combination with subretinal tPA for the management of massive SMH. This could be a safe and effective method to treat such sight-threatening condition. Another key factor is that vascular endothelial growth factor (VEGF) binding ability of the brolucizumab was not compromised when used after vitrectomy.

CASE REPORT

A 60-year-old female presented to us with no known systemic illness, she experienced sudden painless vision loss in the left eye (LE) for one week. At presentation, her best-corrected visual acuity (BCVA) was 6/6, N6, and counting fingers close to face in the right and LE, respectively. Intraocular pressure was 16 mmHg in both eyes. Both eye's anterior segment was within normal limits. No similar complaint was noted in the past. Fundus examination of the LE [Figure 1a] demonstrated a large SMH of more than four disc diameter whereas the right eye showed normal fundus. Spectral-domain optical coherence tomography (SD-OCT) CIRRUS™ HD-OCT (model 5000, Carl Zeiss meditec, Inc., Dublin, CA) [Figure 1b] showed a large fibrovascular pigment epithelium detachment (FVPED) and significant subretinal fluid (SRF) juxtafoveally. Fundus fluorescein angiography [Figure 1c] revealed leakage from the undetermined source superotemporal to the fovea in the late phase. The diagnosis was confirmed with indocyanine green angiography which showed active polyps and subfoveal branching of vascular network [Figure 1d]. We performed a standard 25 G PPV using Constellation® Vision System (Alcon, Fort Worth, Texas). Intravitreal triamcinolone acetonide-assisted vitrectomy was done without base excision. A vial containing 20 mg of Actilyse powder (Alteplase, Boehringer, Ingelheim, International GmbH) was taken and 10 millimeters (mL) of distilled water was added into it. After that, 0.25 mL of this solution was taken in a tuberculin syringe, and 0.75 mL of distilled water was added to make it 1 mL. Out of this one ml solution, 0.9 mL was discarded so that 0.1 mL remains in the tuberculin syringe.

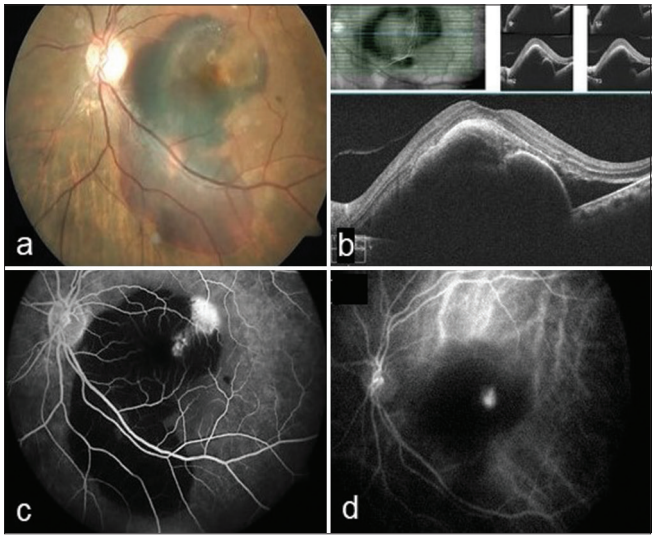

Figure 1: (a) A massive submacular hemorrhage. (b) Large fibrovascular pigment epithelium detachment and subretinal fluid. (c) Late leakage of an undetermined source superotemporal to the fovea. (d) A branching vascular network with active polyps.

Technique used to inject subretinal tPA

A 30-gauge needle was attached to the syringe. A 41-gauge needle with attached silicone tubing was taken; then, the diluted tPA solution from the tuberculin syringe was injected into the silicone tubing of the 41-gauge needle from its rear end. The rear end of the silicone tubing was then attached to the viscous fluid control (VFC) Pak of the Constellation Vision System (Alcon). The VFC injection pressure was kept at 5 mm of Hg and the foot pedal of the constellation machine was slowly depressed to bring tPA solution in the silicone tubing to the tip of the 41-gauge needle. Then the 41-gauge needle was introduced into the vitreous cavity through the 25-gauge port by the surgeon. Under direct visualization, the tip of the 41-gauge needle was introduced subretinally at the point of highest elevation of the retina at an extra macular location. After ensuring that the tip of the needle was subretinal, the foot pedal of the constellation system was gently depressed and 50 µg (0.1 mL) of tPA solution was injected subretinally in a controlled fashion. This was confirmed by the elevation of the retina at the site of injection. After this, fluid gas exchange was performed and an isoexpansile mixture of C3F8 gas (14%) was injected into the vitreous cavity. At the end of the procedure, IVI of brolucizumab (0.05 mg/0.1 mL) was injected. The patient was instructed to maintain supine position for 2 hours (h) followed by prone positioning for one week.

One month after the procedure, additional two loading doses of IVI of brolucizumab were given one month apart. After the third loading dose, her BCVA improved to 6/9, N6. SD-OCT revealed resolved SRF and significantly flattened FVPED [Figures 2a and b]. Henceforth, three months later recurrent SRF was noted with a dropped BCVA, that is, 6/18, N8. Considering the circumstances, fourth and fifth doses of IVI of brolucizumab were given at intervals of three months between the injections. However, one month after the fifth dose, BCVA was found to be stable, but SD-OCT showed fresh trace SMH, reduced FVPED height, subfoveal scar, and no SRF/intra-retinal fluid (IRF) were noted [Figures 3a and b]. In view of fresh trace SMH, the patient was advised

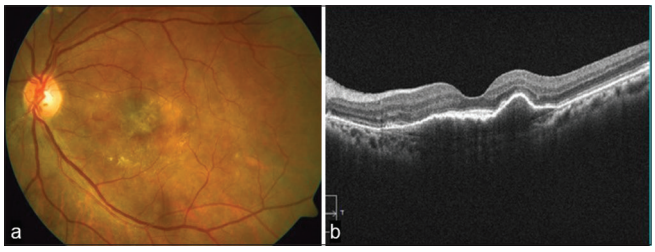

Figure 2: (a) Fundus photograph at three months follow-up shows significantly reduced submacular hemorrhage. (b) Optical coherence tomography macula shows flattened fibrovascular pigment epithelium detachment and resolved subretinal fluid.

to repeat IVI of brolucizumab but the patient refused to take the injection during this visit. Then, she returned to us two months later with organized subfoveal hemorrhage, SRF, IRF, and stable BCVA. Following this, she took the sixth dose of IVI of brolucizumab and one month later her BCVA improved to 6/12, N8 with resolved SRF. After this, she was lost to follow-up for three months and presented with reduced visual acuity, that is, 6/24, N18, increased IRF and SRF with scarred choroidal neovascular membrane (CNVM) in her LE. Consequently, the seventh dose of IVI of brolucizumab was given, and post one month, her BCVA was stable with resolved SRF and IRF. Hereafter, the patient reviewed back after three months from the seventh dose with declined vision, that is, 6/36, N18. Fundus photography and SD-OCT showed increased IRF and SRF compared to the last visit with recurrence of CNVM. Ultimately, she was instructed to take repeat IVI of brolucizumab and she is lost to follow-up since then.

DISCUSSION

In our case report, we determine the safety and efficacy of IVI of brolucizumab, along with subretinal tPA injection through vitrectomy and non-expansile gas injection for the management of massive SMH. Our result also shows the standard action of IVI of brolucizumab even in a vitrectomized eye.

Massive SMH secondary to PCV is an uncommon manifestation that can cause irreversible damage to the photoreceptors.[3] It must be treated instantaneously to avoid permanent loss of vision in the affected eye.[4] Various treatment modalities are available for SMH, depending on the size and duration of the hemorrhage including anti-VEGF injection monotherapy, pneumatic displacement along with anti-VEGF, and/or tPA injection.[3,4] A study conducted by Lin *et al*.[1] including 20 patients with SMH in association with PCV, out of which five patients were treated with subretinal tPA along with vitrectomy and rest 15 patients were treated with IVI of tPA with gas. In addition to the combination therapy, few patients received photodynamic therapy and IVI of anti-VEGF to treat underlying PCV. They concluded that the combination therapy may show favorable anatomic and visual improvements. Kitagawa *et al*.,[5] in a consecutive case series, considering 20 eyes revealed that IVI of recombinant tPA, ranibizumab, and gas is beneficial in the displacement of SMH. Chakraborty and Sheth,[3] in their case series, reported that the intravitreal brolucizumab (IVB) along with SF6 gas and intravitreal tPA is efficacious and safe for the management of massive SMH secondary to macular neovascular disease. In a prospective, interventional case series Kimura *et al*.[6] treated 15 eyes with SMH >1500 microns in PCV patients using vitrectomy and subretinal tPA injection followed by intravitreal anti-VEGF therapy which they found as a promising strategy for improving visual acuity. Similarly, our case report shows long-term favorable anatomical and visual outcomes for massive SMH. Ogura *et al*., in their study, demonstrated the effectiveness of intravitreal brolucizumab injections administered every 12 weeks or 8 weeks for improving and stabilizing visual acuity in Japanese eyes with PCV. These results were comparable to every 8-week dosing interval for intravitreal aflibercept. They also found that brolucizumab had better anatomical outcomes than aflibercept.[7] It could be an effective and safe combination therapy for the acute management of large SMH secondary to PCV. Stanescu-Segall *et al*.[8] reviewed five publications involving 681 eyes and found that the rate of displacement of SMH was 76%. They reviewed the data of several therapies and found that all combination therapies for SMH showed visual improvement, but the best improvement was observed with a combination of anti-VEGF therapy along with rtPA and gas. Gabrielle *et al*. compared the outcomes of pneumatic displacement and PPV, along with tPA and anti-VEGF therapy and achieved similar clinical outcomes from both strategies.[9] Lee *et al*.,[10] in their study, demonstrated that vitreous VEGF levels tend to decrease after PPV. Vitreous VEGF half-lives were found to be ten folds shorter in vitrectomized eyes compared to non-vitrectomized eyes of rabbits. Another study by Kakinoki *et al*.[11] showed that the efficacy of intravitreal bevacizumab was decreased by 60% in macaque eyes following PPV. In contrast, the efficacy of IVI of brolucizumab even after PPV was not decreased. In our case, brolucizumab was found safe and effective even in a vitrectomized eye with dosing intervals comparable to a non-vitrectomized eye. It is evident that the long-term visual outcome greatly depends on the activity of the underlying pathology, which remains unaffected by the displacement of the blood.[12] Cystic changes seen in the optical coherence tomography were indicative of recurrent CNVM which was well managed with brolucizumab monotherapy. Hence, no additional steroid implant was administered. Early detection of potential recurrence after treatment and administration of IVI of brolucizumab whenever required is necessary to preserve visual acuity.

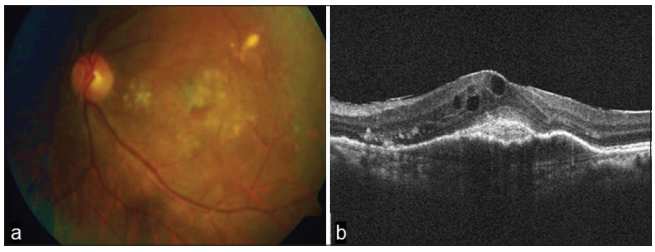

Figure 3: (a) Fundus photograph and optical coherence tomography (OCT) macula one month after the fifth dose of IVB shows scarred fibrovascular pigment epithelium detachment with ERM. (b) OCT of macula shows no subretinal fluid seen below the fovea, sub-foveal scar, SHRM sub-foveally. ERM: Epiretinal membrane, SHRM: subretinal hyper-reflective material, IVB: Intravitreal brolucizumab.

CONCLUSION

In conclusion, the above mentioned procedure can be considered to achieve good anatomical visual results in case of massive submacular hemorrhage.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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