Retinal Detachment Despite Aggressive Management of Aggressive Posterior Retinopathy of Prematurity

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ABSTRACT

Posterior retinopathy of prematurity (ROP) is unusual in its atypical features and its aggressive, rapidly progressive course. It is more difficult to recognize and to treat, with many of these eyes progressing to retinal detachment despite multiple treatments with laser or cryotherapy. The authors present a case of aggressive posterior ROP refractory to multiple laser treatment. This patient was successfully treated with intravitreal bevacizumab, but required repeat treatment 4 months later. The second injection with bevacizumab was followed by progression to retinal detachment requiring surgery. The patient remains stable after surgery. [J Pediatr Ophthalmol Strabismus 2010;47:e1-e4.]

INTRODUCTION

Retinopathy of prematurity (ROP) continues to be a major cause of childhood blindness despite advances in treatment and earlier intervention. Modern neonatal care has allowed for the survival of progressively more premature and low birth weight infants, including the smallest and the youngest, the micro-prematures. Additionally, more ROP has begun to present posteriorly. Nearly 23% of eyes with pre-threshold ROP in the Early Treatment of Retinopathy of Prematurity (ETROP) study had zone I disease compared to just 9.6% in the earlier Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study.

Posterior ROP is difficult to treat with many eyes progressing to stage 4 and 5 ROP even after treatment. In both the CRYO-ROP and the ETROP studies, eyes with zone I ROP responded poorly to both cryotherapy and laser ablative treatment. Flynn and Chan-Ling recently proposed a different pathophysiologic mechanism for zone I disease to account for the poor treatment response of these eyes to laser ablation.

Like other proliferative retinopathies, ROP is thought to be driven by the production of angiogenic factors such as vascular endothelial growth factor (VEGF) by inadequately perfused or hypoxic retina. Accordingly, VEGF levels have been shown to be elevated in the vitreous of eyes with active ROP. It is thought that ablating the peripheral avascular retina targets the source of VEGF, decreasing the drive for neovascularization. In many eyes, posterior ROP progresses despite treatment of the presumed source of VEGF.

To explain this discrepancy, Flynn and Chan-Ling suggested a two-phase process of retinal vascularization: vasculogenesis, which occurs independent of VEGF, and angiogenesis, which is driven by increased levels of VEGF. In zone I ROP, the earlier onset of disease is thought to interrupt the VEGF independent process of vasculogenesis rather than angiogenesis, explaining the lack of response to standard treatment. They also suggested that anti-VEGF therapy such as bevacizumab may succeed where ablative therapy fails by inhibiting tyrosine kinase proteins, thereby attacking the process of abnormal vasculogenesis upstream from VEGF.

Intravitreal bevacizumab has been used recently to treat ROP as both salvage and primary therapy. Herein, we present a case of the off-label use of in-
travitreal bevacizumab in aggressive posterior ROP refractory to multiple laser treatments.

CASE REPORT

A 26-week quadruplet and 860-gram premature neonate was initially evaluated at the Bascom Palmer Institute/Jackson Memorial Hospital at 34 weeks post menstrual age. The neonate was observed as recommended by the ETROP study until bilateral posterior zone II, stage 3+ aggressive posterior ROP disease was diagnosed at 37 weeks post menstrual age. Both eyes were treated within 24 hours with diode laser photo-coagulation in a continuous/dense laser pattern. Likely due to hypopigmentation of the fundus, the power settings in this child were high, especially in the posterior treatment. Two weeks later, additional laser was given in the right eye posterior to the initial treatment for persisting plus disease and activity at the temporal ridge. At 1 week of follow-up, persisting stage 3+ disease in the right eye prompted a third treatment with laser, up to the temporal extent of the macula. Four and a half weeks after the third treatment, a new area of neovascularization developed posterior to and within an area of previous laser treatment, just outside of zone I (Fig. 1A). At this time, intravitreal bevacizumab (0.625 mg/0.025 mL) was injected in the right eye as an off-label salvage treatment.

The areas of neovascularization regressed during the next 4 weeks (Figs. 1B to 1D) and the patient was stable and observed closely during the next 4 months. Four months after treatment with intravitreal bevacizumab, temporal stage 3+ ROP recurred in the right eye with an area of elevation, again within the area of previous laser treatment. After discussion with the parents, a repeat injection of intravitreal bevacizumab was given in the clinic. Two weeks following treatment, the patient developed stage 4B ROP in the right eye (Fig. 2), which was successfully treated with a scleral buckle, lens-sparing pars plana vitrectomy, endolaser, and 1,000-centistoke silicone oil.

The patient did well until postoperative month 3, at which time he developed a recurrent retinal detachment. He underwent a subsequent re-operation with silicone oil and intraoperative injection of intravitreal bevacizumab (0.625 mg/0.025 mL). The retina finally stabilized and has remained so, up to the last follow-up at 1½ years. Aggressive amblyopic management is currently in place and successful, with both eyes showing fix-and-follow behavior without any significant eye preference.

DISCUSSION

Aggressive posterior ROP is unusual in its atypical features and its aggressive, rapidly progressive
It can be more difficult to recognize and to treat, with many of these eyes progressing to retinal detachment despite multiple treatments with laser or cryotherapy. This lack of response has prompted a search for other treatment modalities, namely anti-VEGF agents. Although some have used anti-VEGF treatment as salvage therapy after failure of conventional treatment, others have used it as primary treatment, with one series showing complete resolution of disease after a single injection of bevacizumab. However, duration of follow-up varied widely in this study, ranging from 13 to 85 weeks with a mean of 48.5 weeks. In our case, ROP recurred 4 months after initial treatment with bevacizumab, requiring a repeat injection.

In contrast to other proliferative retinopathies, neovascularization in ROP is believed to be caused by a burst of VEGF rather than a continuous production. Thus, treating the eye at the time of this burst would theoretically obviate the need for further treatment. However, Flynn and Chan-Ling have suggested that posterior ROP may be a different disease from typical ROP, with a pathophysiologic mechanism independent of VEGF. This may explain the recurrence of neovascularization seen in our case and in several other reports. It also underscores the need for a better understanding of aggressive posterior ROP and the necessity of long follow-up in these eyes.

In a recent review of 85 eyes with varying degrees of ROP treated with bevacizumab, the majority (74 eyes) remained stable or regressed. However, of the 17 eyes that had aggressive posterior ROP, 3 (18%) progressed to retinal detachment.

Flynn and Chan-Ling’s hypothesis of a VEGF independent process in zone I disease may help explain why many eyes with aggressive posterior ROP progress despite treatment. However, because most eyes do respond to targeted treatment of VEGF, other factors may be involved. It is possible that VEGF is inadequately blocked in some cases and requires higher doses of bevacizumab; it has been suggested that VEGF production is more potent in severe ROP. "There may also be persistent production of VEGF in these eyes. Fluorescein angiography in eyes with aggressive posterior ROP has shown absent capillary beds and arteriovenous shunting throughout the vascularized retina, including the posterior pole. These areas of the retina may potentially be a continued source of VEGF.

After repeat treatment with bevacizumab, our patient progressed rapidly, within 2 weeks, to stage 4B ROP. Although it is not clear whether bevacizumab was causative in our case, others have also reported this phenomenon, although it occurred much more rapidly in those cases. A similar effect has been noted in eyes with active proliferative diabetic retinopathy after treatment with intravitreal bevacizumab and is believed to be caused by rapid involution of neovascularization with fibrosis and contraction of the posterior hyaloid. In our case, we did not notice significant fibrosis associated with the stage 3 neovascularization prior to injection of bevacizumab.

Intravitreal bevacizumab for the treatment of aggressive posterior ROP is promising. Our case supports a growing number of reports showing dramatic regression of neovascularization after treatment with bevacizumab, particularly after conventional treatment has failed. However, as in our case, multiple treatments may be necessary in aggressive posterior ROP, possibly due to factors other than VEGF driving this particular type of ROP. Another possibility is that the dose of bevacizumab (0.625 mg/0.025 mL) we injected was not adequate; others have injected up to 1.25 mg. Prospective, randomized, and controlled studies are currently under way and will help determine the safety and efficacy of this emerging treatment for ROP. Further basic

Figure 2. Progression to stage 4B retinopathy of prematurity 2 weeks after a second injection of bevacizumab for recurrent stage 3+ retinopathy of prematurity.
science and clinical studies are needed to better understand aggressive posterior ROP and the role of bevacizumab in the disease, whether as primary, salvage, or combination treatment.

REFERENCES