A Rare Association of Intravitreal Bevacizumab Injection With Double Ridge Formation in Retinopathy of Prematurity

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ABSTRACT

A second anterior ridge formed 8 weeks after therapy in a case of zone II, stage 3 retinopathy of prematurity, which was treated with intravitreal bevacizumab injection alone. The clinical appearance was defined as "double ridge." Retinopathy of prematurity cases treated only with intravitreal bevacizumab injections may progress; therefore, close follow-up is recommended. **[*J Pediatr Ophthalmol Strabismus* 2014;51:e66-e68.]**

INTRODUCTION

Retinopathy of prematurity (ROP) is a major worldwide cause of childhood blindness. According to the Early Treatment of Retinopathy of Prematurity (ETROP) study, low birth weight and gestational age are the major risk factors for ROP formation.[1,2]

ROP comprises an extra-uterine neovascularization of the inner retinal vessels and occurs in two phases. The first phase, from premature birth to 30 weeks post-menstrual age (PMA), is called the vaso-obliterative phase. In this phase, the premature infant enters a hyperoxic environment at birth and then the angiogenic factors induced by hypoxia are down-regulated. Also, the use of anti-vascular endothelial growth factor (VEGF) drugs is contraindicated. The second phase, from 31 to 42 weeks PMA, is the vaso-proliferative phase. In this phase, the peripheral avascular retina becomes hypoxic and metabolically active. Thus, new vessel growth is stimulated and VEGF increases. However, there is an abnormal growth of vessels at the junction of the avascular and vascular retina.[3]

Treatment guidelines have been created based on several multicenter ROP trials. In the Cryotherapy for ROP trial, cryotherapy was applied to the peripheral avascular retina and retinal ablation with laser photocoagulation for type 1 prethreshold ROP was used in the ETROP study.[2] Both cryotherapy and laser photocoagulation are destructive therapeutic models. Intravitreal bevacizumab injections are an alternative therapy based on the role of VEGF in the pathogenesis of ROP. The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) study suggested that VEGF inhibitors are useful in the treatment of ROP. Intravitreal bevacizumab monotherapy in infants with zone I, stage 3 ROP showed a significant benefit. Peripheral retinal vessel development was continued after the intravitreal bevacizumab injections.[4] However, late activation and the progression of ROP after intravitreal bevacizumab monotherapy have been reported.[5,6] We report the development of a second ridge in an ROP case treated with intravitreal bevacizumab injections alone in one eye that progressed to tractional retinal detachment in the other eye.

CASE REPORT

According to medical records, a former 28-week premature, 870-g neonate received intravitreal

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Submitted: June 4, 2014; Accepted: August 5, 2014; Posted online: October 8, 2014
The authors have no financial or proprietary interest in the materials presented herein.
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doi: 10.3928/01913913-20140930-01

bevacizumab injections at 36 weeks PMA in both eyes. Intravitreal hemorrhage, zone II, stage 3 ROP and plus disease were observed in the right eye, and zone II, stage 3 ROP and plus disease were seen in the left eye. During follow-up, the clinical picture in the left eye regressed to a large extent. The appearance of plus disease diminished, the neovascularization and ridge in the nasal quadrant regressed, and the retinal vessels reached zone III. However, the appearance of the ridge was similar in the temporal quadrant at 39 weeks PMA based on the medical reports. On the other hand, the intravitreal hemorrhage and plus disease in the right eye persisted. The weekly examination notes for both eyes were similar until the last visit of the patient at 44 weeks PMA.

The patient was referred to our clinic at 44 weeks PMA with a large preretinal hemorrhage in zone II, traction in the nasal quadrant, and retinal detachment on the temporal side of the right eye. Two days after the referral of the patient, pars plana vitrectomy and lensectomy were performed on the right eye. In the left eye, a preretinal hemorrhage developed between the optic disc and macula and two ridges in the temporal retinal area. The first ridge was between zones I and II, and the second ridge was located more anteriorly, at zone II (**Figure 1**). The retinal vessels passed through the first ridge and ended at the second ridge. In the inferior temporal retinal quadrant of the left eye, vitreous traction was noted. The left eye was successfully treated by the application of laser photocoagulation therapy to the avascular peripheral retina. Weekly examinations were performed throughout the first month after therapy. The progression of the left eye was halted and no reactivation occurred during the 6 months of follow-up.

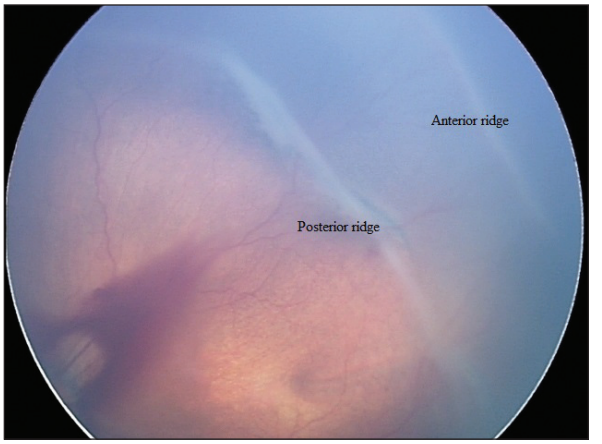

Figure 1. RetCam (Clarity Medical Systems, Pleasonton, CA) photograph of the left eye showing the double ridge formation.

DISCUSSION

VEGF is a key molecule for the pathogenesis of ROP and intravitreal bevacizumab is an alternative therapeutic model for appropriate cases.[4] However, clinical studies on intravitreal bevacizumab in ROP are not yet adequate and more long-term outcomes should be reported.

Recent evidence suggests that monotherapy with intravitreal bevacizumab may be a viable first-line treatment for select cases of zone I ROP and, possibly, for posterior zone II disease.[7] Intravitreal bevacizumab therapy could also be applied for stages 3, 4, and 5 ROP as both a monotherapy or in combination with laser photocoagulation or vitrectomy. The BEAT-ROP study suggested that intravitreal bevacizumab monotherapy is more effective than laser therapy in zone I, stage 3+ cases.[4] Recurrence rates were reported at 42% (14 of 33 infants) for the laser group and 6% (2 of 31 infants) for the bevacizumab group in zone I cases; further, there was a significant difference between the two groups (odds ratio: 0.09; 95% confidence interval [CI]: 0.02 to 0.43; $P = .003$). However, in zone II cases, the rates of recurrence did not differ significantly between the laser and bevacizumab therapy groups (12% [5 of 40 infants] recurrence in laser, 5% [2 of 39 infants] recurrence in bevacizumab, odds ratio: 0.39; 95% CI: 0.07 to 2.11; $P = .27$). For both zones, the mean time to recurrence was 16.0 ± 4.6 weeks for the bevacizumab group and 6.2 ± 5.7 weeks for the peripheral laser therapy group.[4] Accordingly, reactivations after intravitreal bevacizumab injections can occur later, and clinicians should be careful in following up after bevacizumab treatment.

Late reactivation and recurrences of ROP were reported.[5] The mean time to reactivation after intravitreal bevacizumab therapy was 14.4 weeks, with a minimum of 4 and maximum of 35 weeks, whereas retinal detachment developed at a mean of 58.4 weeks PMA.[5] In the BEAT-ROP study, the final examination was performed at 54 weeks PMA, whereas another study ended the examination at 68 weeks PMA.[5] In the current case, reactivation in the left eye and progression in the right eye were documented 8 weeks following the intravitreal bevacizumab injection at 44 weeks PMA. Reinjection

or laser therapy could have been performed for the right eye previously, but the follow-up seemed to be adequate for the left eye. There is a paucity of literature on the long-term effects of intravitreal bevacizumab injections on ROP cases. A single case report series did follow up for 5 years.[8] In that report, low myopia was the only side effect documented in the majority of cases.

The complete regression of neovascularization may occur after intravitreal bevacizumab injection. However, recurrences and reactivations during follow-ups have been reported.[5] In our case, the appearance of a double ridge in one eye and the development of retinal detachment in the other eye is an example of the progression of ROP after intravitreal bevacizumab injection. We suggest that, if bevacizumab injections are not combined with laser photocoagulation, retinopathy can progress as a result.

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