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Late recurrence of retinopathy of prematurity after treatment with both intravitreal bevacizumab and laser

Wendy Chen, MD, PhD^a, Gil Binenbaum, MD, MSCE^{b,c}, Karen Karp, RN, BSN^b, Agnieszka Baumritter, MS^b, Denise J. Pearson, COMT^{b,c}, Albert M. Maguire, MD^{b,c}, and Graham E. Quinn, MD, MSCE^{b,c}

^aDivision of Ophthalmology, Alpert Medical School at Brown University, Providence, Rhode Island

^bDivision of Ophthalmology, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

^cScheie Eye Institute, Department of Ophthalmology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia

Abstract

An infant of 36 weeks' postmenstrual age (PMA) and 25 weeks' gestation received bilateral intravitreal bevacizumab injections for type 1 retinopathy of prematurity. He underwent laser photocoagulation in both eyes 5 days later, confluent except for 1 clock hour obscured by hemorrhage in the left eye. Despite initial regression, neovascularization in both vascularized and lasered retina with plus disease recurred, requiring repeat laser bilaterally at 51 weeks' PMA and vitrectomy in the left eye at 54 weeks' PMA. Whereas late recurrence is thought to occur rarely after laser treatment, infants who have received both bevacizumab injections and laser may still require long-term surveillance for recurrence. In this case, fundus photography proved valuable for appreciating recurrent plus disease because the initial treatments had resulted in marked retinal vessel attenuation.

Case Report

A boy born via emergent C-section following retroplacental hemorrhage at 25 weeks' gestation with birth weight 490 g had a postnatal course including respiratory distress, sepsis, hemodynamic instability, small bowel perforation, ileostomy, bowel reanastomosis, and persistent thrombocytopenia and anemia despite repeated transfusions. Further issues included periventricular leukomalacia, adrenal insufficiency, renal failure, and osteopenia with long bone fractures. Diagnostic examinations for retinopathy of prematurity (ROP) between 30 and 34 weeks postmenstrual age (PMA) revealed immature vasculature in zone I. At 36 weeks' PMA, development of aggressive posterior ROP was suspected, with stage

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Correspondence: Gil Binenbaum, MD, MSCE, Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd., 9-MAIN, Philadelphia, PA 19104 (binenbaum@email.chop.edu).

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3, zone I, and plus disease in the right eye, and stage 3 at the border of zones I and II, and plus disease with localized vitreous hemorrhage in the left eye.

Each eye underwent intravitreal injection of 0.625 mg bevacizumab in 0.025 ml of solution. One week later, some decrease in plus disease was noted with persistent stage 3, and retinal laser photocoagulation was performed in both eyes due to the treating ophthalmologist's concern for the aggressiveness of the disease. The ROP regressed, but the infant's systemic status deteriorated, and he was transferred to our hospital at 43 weeks PMA for management of chronic lung disease, necrotizing enterocolitis, and sepsis.

On first ROP examination at The Children's Hospital of Philadelphia at 43.5 weeks' PMA (Figure 1A–C), the retinopathy appeared to have regressed; no acute ROP was visible, though the vasculature was extremely attenuated and terminated in zone 1. Both optic nerves appeared pale. Near-confluent laser photocoagulation of avascular retina was noted except for <1 clock hour of old vitreous hemorrhage superiorly in the left eye. Serial examinations were undertaken at 1- to 2-week intervals. At 51 weeks' PMA, atypical neovascular growth was detected along the termination of the temporal vascular arcades and in areas of previously lasered avascular retina. In the left eye, a large neovascular frond also developed temporal to the laser skip area. Vessel changes suggestive of plus disease were present in both eyes (Figure 1D–F), with an increase in vascular caliber and tortuosity compared to the previously attenuated vessels. Fill-in laser photocoagulation was performed in both eyes. Over the next 3 weeks, the neovascularization and plus disease regressed in the right eye. However, plus disease persisted in the left eye, and a stage 4A localized tractional retinal detachment developed, gradually progressing to stage 4B involving the central macula (Figure 2). A lens-sparing pars plicata vitrectomy was performed within 2 days of diagnosis of macular detachment, and the retina was successfully reattached (Figure 3).

Discussion

Intravitreal bevacizumab (IVB) has been advocated for treatment of posterior ROP, with reportedly low recurrence compared with laser.^{1,2} Late recurrences of treatment-requiring ROP have been reported following monotherapy IVB,^{3–5} and prolonged clinical follow-up is required.⁶ The addition of laser therapy shortly following IVB and subsequent disease regression may be hypothesized to decrease the risk of recurrence and obviate the need for prolonged follow-up. However, in this case, ROP in the right eye recurred at 51 weeks' PMA (26 weeks of age) despite adequate laser without skip areas. In addition, atypical neovascularization occurred in areas of previously lasered retina. These findings suggest that extended follow-up is necessary despite the addition of laser following recent IVB. In the left eye, the presence of 1 clock hour of laser skip area may have contributed to a worse recurrence and the need for vitrectomy. However, onset of late recurrence was the same in both eyes, and the disease course of the left eye highlights an even greater need for close long-term follow-up in eyes that have received IVB and laser but have even a small skip area. Once a stage 4A detachment was seen, monitoring with increased frequency (every few days) resulted in timely identification of a fovea-threatening macular detachment and successful surgical repair. Inadequate follow-up frequency may result in late detection of fibrous traction bands and limit surgical options.^{3–5}

This case highlights that marked retinal vessel attenuation may be associated with IVB for ROP. Notably, vessel attenuation “resets” the baseline appearance by which vascular changes are subsequently judged with relation to diagnosis of recurrence. The appearance of the retinal vessels at 51 weeks’ PMA did not meet traditional criteria for plus disease, but comparison of serial fundus photographs clearly showed a dramatic increase in vessel caliber and tortuosity. Vessel attenuation may have been less pronounced if lower doses of bevacizumab were used, although this hypothesis requires investigation.

The mechanism of late recurrence following IVB is unclear. One possibility is that normal-appearing vascularized retina actually remains abnormally perfused and a potential continued source of vascular endothelial growth factor (VEGF). This hypothesis is supported by transient postinjection retinal vessel sheathing and leakage on fluorescein angiography.^{3,5,7} In primate models, IVB may result in occlusive thrombosis of choriocapillaris by immune complex deposition,⁸ leading to death of overlying photoreceptors. A similar microangiopathic mechanism may contribute to ischemic optic nerve injury. The present case had optic pallor noted on transfer to our hospital. This finding, usually seen in infants with complicated medical courses including periventricular leukomalacia, has also been reported following IVB for ROP,⁵ and ischemic optic neuropathy (ION) following IVB in adults with or without ION risk factors is reported.^{9,10} Reduction of normal neuroprotective effects of VEGF by bevacizumab⁹ or alteration of autoregulation of blood flow to the optic nerve¹⁰ are proposed mechanisms.

This case illustrates that IVB may be associated with late and atypical ROP recurrences despite adjuvant early laser treatment. Optic nerve ischemia and marked vessel attenuation can mask recurrent plus disease unless close attention is paid to relative changes in vessel appearance.

Acknowledgments

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FIG 1.

Fundus appearance on RetCam photography (Clarity Medical Systems Inc, Pleasanton CA) following treatment with intravitreal bevacizumab and laser photocoagulation at 36–37 weeks' postmenstrual age (PMA). At 44 weeks' PMA, there is vascular attenuation in the right (A) and left (B) eyes and a laser skip area underlying old vitreous hemorrhage superiorly in the left eye (C). At 51 weeks' PMA (D, right eye; E–F, left eye), atypical neovascularization (arrows) has developed in areas of previously lasered retina and at the edge of vascularized retina, with plus disease–like changes (arrowheads) seen as a marked change in vessel caliber and tortuosity compared with earlier photographs.

FIG 2.

Fundus appearance at 55 weeks' PMA, following retreatment laser photocoagulation at 51 PMA. Regressing ROP in the right eye (A) but persistent plus disease and tractional retinal detachment (arrows) involving the macula in the left eye (B).

FIG 3.

Fundus appearance at 59 weeks' PMA, following retreatment laser photocoagulation at 51 weeks' PMA in both eyes and lens-sparing vitrectomy in the left eye. ROP has regressed in both eyes (A, right eye; B–C, left eye) without retinal detachment. Areas of regressed neovascularization in the right eye are marked with arrow heads.