Short Communication

Reactivation of Aggressive Retinopathy of Prematurity Following Intravitreal Bevacizumab

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ABSTRACT

Aggressive Retinopathy of Prematurity (A-ROP) is a severe and rapidly progressing form of ROP that can lead to blindness if not managed effectively. Intravitreal Bevacizumab injection has emerged as a primary treatment option for A-ROP; however, the risk of recurrence necessitates vigilant follow-up and management. We present a case of 5-week-old premature male infant, diagnosed with bilateral A-ROP during routine screening and received an intravitreal Bevacizumab injection. Initial treatment resulted in clinical improvement, but one month later, the patient developed fibrosis, traction, and retinal neovascularization in the right eye, while the left eye showed signs of regression. Laser photocoagulation therapy was subsequently administered to manage the disease progression. This case report underscores the complexities in managing A-ROP, particularly the potential for reactivation following Bevacizumab treatment. A combined therapeutic approach, including laser photocoagulation, may be necessary to achieve optimal control of A-ROP progression.

Key Words: Anti-VEGF, Bevacizumab, Retinopathy of Prematurity, Aggressive Retinopathy of Prematurity, Vascular Endothelial Growth Factor

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INTRODUCTION

Aggressive Retinopathy of Prematurity (A-ROP) represents a severe variant of retinopathy of prematurity (ROP) that progresses rapidly and can lead to blindness if not managed promptly. Despite advancements in neonatal care, ROP remains a significant challenge, particularly in regions like Indonesia, where the prevalence of premature births is high.[1,2] The pathophysiology of A-ROP is complex, involving the dysregulation of retinal angiogenesis in the context of premature birth and fluctuating oxygen levels. In preterm infants, the incomplete development of retinal blood vessels leads to a state of relative hypoxia, triggering a cascade of events that result in abnormal neovascularization.[3] Anti-VEGF agents like Bevacizumab target this pathological process by inhibiting VEGF, a key mediator of abnormal blood vessel growth. However, despite their targeted action, these agents do not fully address the underlying retinal immaturity and hypoxia, which can lead to recurrence or progression of the disease. Furthermore, the systemic absorption of anti-VEGF agents raises concerns about potential adverse effects on the developing organs of preterm infants, making their use a subject of ongoing debate in neonatal care.[4]

The management of ROP has traditionally relied on laser photocoagulation, but the introduction of anti-VEGF therapy, such as Bevacizumab, has become increasingly popular due to its effectiveness in halting abnormal blood vessel growth.[5]However, the risk of recurrence remains a significant concern, requiring careful long-term management. This case report discusses the clinical course of a premature infant with A-ROP treated with intravitreal Bevacizumab, who

subsequently developed recurrent disease. The objective of this report is to highlight the challenges in managing A-ROP, particularly in the context of recurrence after anti-VEGF therapy, and to emphasize the importance of a tailored approach to treatment and long-term monitoring in these vulnerable patients.

Case Description

A male infant, born at 30 weeks gestation with a birth weight of 1,215 grams, was referred to the neonatal unit of a tertiary hospital in Bali, Indonesia for ROP screening at 28 days of age. The infant's medical history was complex, including severe asphyxia, respiratory distress secondary to neonatal pneumonia, sepsis, meningitis, and necrotic wound secondary to phlebitis. These conditions necessitated intensive care, including oxygen therapy with a High Flow Nasal Cannula (HFNC) for three days, as well as antibiotic treatments.

At the time of screening, the infant's chronological age was 4 weeks, with a post-menstrual age (PMA) of 34 weeks, and a body weight of 1,395 grams. Fundus imaging revealed minimal round haemorrhages in the superotemporal quadrant of Zone I in both eyes, along with arterial tortuosity in one quadrant of the left eye. The absence of a demarcation line or ridge suggested the early stages of ROP, leading to a diagnosis of pre-plus disease OU (Figure 1a, 1b). A follow-up examination one week later (PMA 35 weeks) showed an increase in retinal haemorrhages and the development of arterial tortuosity and venous dilation in all quadrants of both eyes (Figure 2a, 2b). These findings led to a diagnosis of Aggressive Posterior Retinopathy of Prematurity (A-ROP) in both eyes.

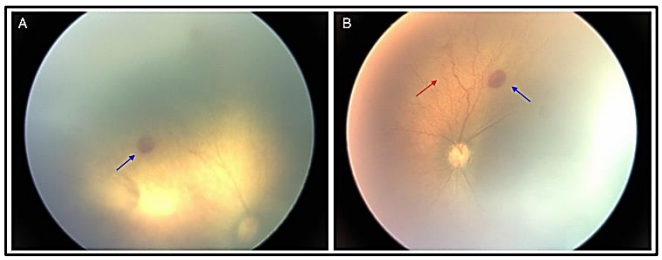

Figure 1: Fundus photo of both eyes showing immature retina consistent with pre-plus disease. Blue arrows point to retinal haemorrhages. Red arrow points to arterial tortuosity on superotemporal quadrant.

Intravitreal Bevacizumab (0.625 mg/0.025 ml) was administered in both eyes under local anaesthesia. The injection procedure was performed at 1 millimetre posterior to the limbus aimed at the optic nerve direction. Post-injection, the infant was monitored closely, with no immediate complications such as fever, respiratory distress, or signs of ocular infection. The infant's visual response was appropriate for age, and follow-up of fundus imaging 12 days post-injection indicated a reduction in retinal haemorrhages and vascular tortuosity without the development of new retinal pathology.

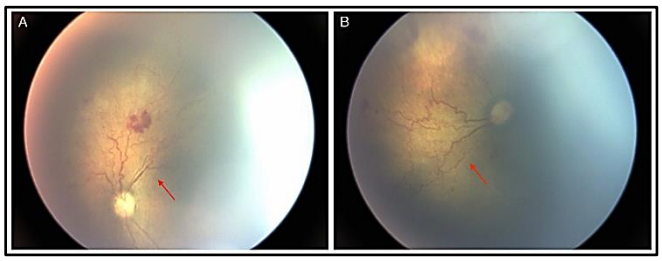

Figure 2: Fundus photo one week after observation. Red arrow points to arterial tortuosity and venous dilation in both eyes.

At one-month follow-up (PMA 39 weeks), significant differences in treatment response between the two eyes became apparent. The left eye showed stable ROP regression, but the right eye developed peripheral retinal fibrosis and traction, indicative of reactivation of A-ROP (Figure 3a). Laser photocoagulation was performed on the right eye, targeting the avascular anterior retina to control further disease progression. Despite this intervention, follow-up imaging five days post-laser therapy revealed persistent fibrosis, neovascularization, and vitreous traction in the right eye (Figure 3b), necessitating consideration of further surgical options, such as pars plana vitrectomy (PPV). However, the decision was made to focus on supportive care and regular monitoring, with the right eye eventually deemed non-operable.

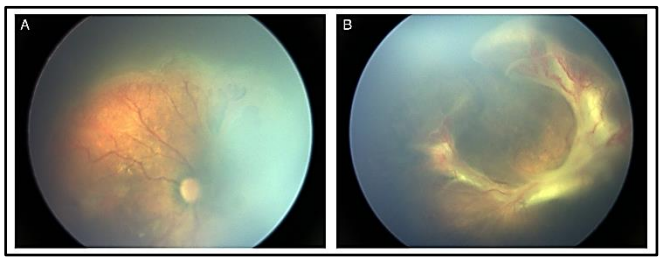

Figure 3: Right eye. A: Fundus photo at one month following Bevacizumab injection. B: Progression of A-ROP despite multimodal treatments with laser photocoagulation.

DISCUSSION

ROP results from an imbalance in retinal vascular growth, primarily due to fluctuating oxygen levels that lead to retinal hypoxia and subsequent abnormal neovascularization. The introduction of anti-VEGF therapies, such as Bevacizumab, has provided an alternative to traditional laser photocoagulation, particularly for posterior ROP cases where laser treatment is challenging.[5,6] However, while Bevacizumab effectively inhibits VEGF, reducing abnormal vascular growth, it does not entirely prevent recurrence, as seen in this case.[4]

Recurrence of ROP following anti-VEGF therapy is influenced by several factors, including the initial severity of the disease, the extent of retinal neovascularization, and the infant's overall health and systemic conditions. Studies have shown that younger gestational age at birth, lower birth weight, and the presence of systemic infections like sepsis are significant risk factors for recurrence.[7,8] Additionally, the presence of extensive retinal neovascularization at the time of anti-VEGF injection is a critical predictor of recurrence. In this case, the patient's very low birth weight, history of sepsis, and the presence of aggressive retinal neovascularization likely contributed to the recurrence observed in the right eye. Furthermore, the timing of recurrence can vary, with some cases presenting within weeks of the initial treatment, while others may recur months or even years later, necessitating prolonged monitoring.[9]

Anti-VEGF therapy offers several advantages over traditional laser photocoagulation in the management of A-ROP. One of the primary benefits is the ability of anti-VEGF agents to target the entire retina, including the posterior pole, where laser therapy may be less effective due to technical limitations or the risk of damaging central vision.[10] Bevacizumab and other anti-VEGF agents work by inhibiting VEGF, thereby reducing abnormal blood vessel growth and potentially preserving more of the peripheral and central retina compared to laser therapy, which ablates the peripheral retina to reduce VEGF production. Additionally, studies have shown that anti-VEGF therapy may result in better visual outcomes and less severe refractive errors compared to laser photocoagulation, particularly in cases involving Zone I disease.[5]However, despite these benefits, anti-VEGF therapy does not eliminate the need for careful and continuous follow-up due to the risk of recurrence.

Given the risk of recurrence and the limitations of both anti-VEGF and laser therapies, a multimodal approach combining both treatments have been increasingly advocated for managing severe cases of A-ROP. This approach takes advantage of the strengths of each modality: anti-VEGF therapy to address abnormal neovascularization and laser photocoagulation to reduce the retinal area producing VEGF.[3] Combining these therapies may provide better control of the disease, reducing the risk of recurrence and preserving visual function. In cases where recurrence is detected, as in this patient, the addition of laser photocoagulation can help stabilize the retina and prevent further progression of the disease. The decision to use a multimodal approach should be individualized based on the disease severity, the location of neovascularization, and the overall health of the infant, emphasizing the importance of a tailored treatment plan in managing A-ROP.[10]

Despite the insights provided by this case, several limitations must be acknowledged. Firstly, this report is based on a single case, limiting the generalizability of the findings. The outcomes observed in this patient may not be universally applicable, particularly given the complex interplay of factors that influence ROP progression and treatment response. Additionally, the long-term effects of anti-VEGF therapy in preterm infants remain unclear, with ongoing concerns regarding potential systemic impacts on developing organs. Future studies involving larger cohorts and long-term follow-up are necessary to better understand the efficacy and safety of combining anti-VEGF therapy with laser photocoagulation in A-ROP management. Moreover, the availability and accessibility of these treatments in different healthcare settings can vary, potentially influencing the outcomes and feasibility of such multimodal approaches in resource-limited environments.

CONCLUSION

This case emphasizes the challenges of managing A-ROP, particularly regarding the risk of recurrence following anti-VEGF therapy. While Bevacizumab is effective in initial disease control, it does not eliminate the risk of recurrence, necessitating vigilant follow-up and consideration of combination therapies, such as laser photocoagulation, to manage severe cases. Long-term management should also include regular vision assessments and early identification of refractive errors to optimize visual outcomes and prevent long-term visual impairment.

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REFERENCES

1. **Blencowe H, Lawn JE, Vazquez T, Fielder A, Gilbert C.** Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res. 2019;**74(Suppl 1):**35-49.Doi: 10.1038/pr.2013.205.
2. **Edy Siswanto J, Sauer PJ.** Retinopathy of prematurity in Indonesia: Incidence and risk factors. J Neonatal Perinatal Med. 2017;**10(1):**85-90. Doi: 10.3233/npm-915142.
3. **Ryu J.** New Aspects on the Treatment of Retinopathy of Prematurity: Currently Available Therapies and Emerging Novel Therapeutics. Int J Mol Sci. 2022;**23(15):**8529. Doi: 10.3390%2Fijms23158529.
4. **Murakami T, Okamoto F, Kinoshita T, Shinomiya K, Nishi T, Obata S, et al.**Comparison of long-term treatment outcomes of laser and anti-VEGF therapy in retinopathy of prematurity: a multicenter study from J-CREST group. Eye (Lond). 2023;**37(17):**3589-3595. Doi: 10.1038/s41433-023-02559-z.
5. **Mintz-Hittner HA, Geloneck MM, Chuang AZ.** Clinical management of recurrent retinopathy of prematurity after intravitreal bevacizumab monotherapy. Ophthalmology.2016;**123(9):**1845-1855. Doi: 10.1016/j.ophtha.2016.04.028.
6. **Wang SD, Zhang GM.** Shenzhen Screening for Retinopathy of Prematurity Cooperative Group. Laser therapy versus intravitreal injection of anti-VEGF agents in monotherapy of ROP: a Meta-analysis. Int J Ophthalmol. 2020;**13(5):**806-815. Doi: 10.18240%2Fijo.2020.05.17.
7. **Fadakar K, Mehrabi Bahar M, Riazi-Esfahani H, Azarkish A, Farahani AD, Heidari M, et al.**Intravitreal bevacizumab to treat retinopathy of prematurity in 865 eyes: a study to determine predictors of primary treatment failure and recurrence. Int Ophthalmol. 2022;**42(7):**2017-2028. Doi: 10.1007/s10792-021-02198-x.
8. **Lyu J, Zhang Q, Chen CL, Xu Y, Ji XD, Li JK, et al.** Recurrence of Retinopathy of Prematurity After Intravitreal Ranibizumab Monotherapy: Timing and Risk Factors. Invest Ophthalmol Vis Sci. 2017;**58(3):**1719-1725. Doi: 10.1167/iovs.16-20680.
9. **Wu FY, Yu WT, Zhao DX, Pu W, Zhang X, Gai CL.** Recurrence risk factors of intravitreal ranibizumab monotherapy in retinopathy of prematurity: a retrospective study at one centre. Int J Ophthalmol. 2023;**16(1):**95-101. Doi: 10.18240%2Fijo.2023.01.14.
10. **Hartnett ME, Stahl A.** Laser versus Anti-VEGF: A Paradigm Shift for Treatment-Warranted Retinopathy of Prematurity. Ophthalmol Ther. 2023;**12(5):**2241-2252. Doi: 10.1007/s40123-023-00744-7.

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