Post-Ranibizumab injection endophthalmitis in aggressive posterior retinopathy of prematurity

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A preterm infant with zone 1 aggressive posterior retinopathy of prematurity developed infectious endophthalmitis after intravitreal injection of ranibizumab. Urgent empirical intravitreal therapy with vancomycin, ceftazidime, and dexamethasone along with intravenous therapy with amikacin and meropenem helped in early resolution. Vascularization/activity of disease subsided on follow-up, media cleared, and laser photocoagulation was completed. Later the disease reactivated, developed vitreous membranes and central retinal traction, for which 25-gauge lens-sparing vitrectomy was performed. Emergent treatment helped in salvaging the eye from both aggressive ROP disease and devastating endophthalmitis. Rationale approach to such a case is being discussed.

Key words: Endophthalmitis, ranibizumab, retinopathy of prematurity, vascular endothelial growth factor

The use of anti-vascular endothelial growth factor (VEGF) agents is an emerging treatment for retinopathy of prematurity (ROP). Bevacizumab eliminates the angiogenic threat of ROP (BEAT-ROP) study has shown the benefits of intravitreal use of these agents in Stage 3+ disease in zone 1 and 2.[1] Thereafter, the off-label use of these agents has widely increased in ROP.

Infectious endophthalmitis is the most devastating complication of intravitreal anti-VEGF injections.[2] To the best of our knowledge, only a single report exists on infectious endophthalmitis after anti-VEGF injection in ROP, which described the early clinical characteristics and benefit of early intravitreal antibiotic injection.[3] We here report the course of disease in a case of post-ranibizumab injection endophthalmitis in aggressive posterior ROP (APROP) disease and discuss the management approach.

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Case Report

A male infant born at 31 weeks with birth weight of 1350 g was diagnosed elsewhere with zone 1 APROP in both eyes at 4 weeks of life (postconceptional age [PCA] 35 weeks). As per referral records, intravitreal injection of ranibizumab (0.25 mg) was given in the left eye in operation theater (OT) under sedation with strict aseptic precautions. At day 4 after injection, conjunctival congestion, hypopyon, and vitritis were noted in the left eye suggestive of infectious endophthalmitis. Empirically intravitreal injection of vancomycin (0.5 mg), ceftazidime (1 mg), and dexamethasone (200 µg) was given in the left eye (all half of the adult dosage). A dry vitreous tap was noted before intravitreal injection. Intravenous meropenem (40 mg BD) and amikacin (15 mg BD) were also started after sending sample for blood culture. Later, blood culture for bacterial sepsis turned out to be sterile. Intravitreal injection of ranibizumab (0.25 mg) was given in the right eye under similar OT conditions at 36 weeks' PCA (after 5 days of starting endophthalmitis treatment) followed by partial laser photocoagulation. Thereafter, the child was shifted to our center for further management.

In between, the child was brought once to our center on day 6 after injection for the second opinion, when fundus imaging revealed signs suggestive of resolving endophthalmitis in the left eye [Fig. 1a]. At 37 weeks' PCA, we observed that the right eye had zone 1 APROP with decreasing plus disease with mild central traction with laser scars [Fig. 2a]. The left eye had clear anterior chamber, resolving vitritis, and zone 1 disease with mild central traction. Intravenous antibiotics were continued for a total of 10 days. The media cleared well and laser photocoagulation was completed in both eyes in two sittings. On follow-up (42 weeks), the neovascularization regressed in both eyes with persistent low central traction [Figs. 1b and 2b]. At 48 weeks, reactivation of disease with sudden worsening of central tractional retinal detachment (TRD) was noted in the left eye [Fig. 1c]. After obtaining informed consent from the parents, 25-gauge lens-sparing vitrectomy was performed in the left eye at 49 weeks' PCA. The vitreous membranes were removed and central traction over the disc was relieved. Since surgery was performed 14 weeks after starting treatment of endophthalmitis, vitreous sample was not sent for microbiological analysis. Six weeks after surgery, the left eye had regressed disease with clear media and sequelae in the form of puckered posterior retina [Fig. 1d].

Discussion

Antiangiogenic therapy has numerous advantages over laser treatment in active ROP.[1] However, safety is the reason for

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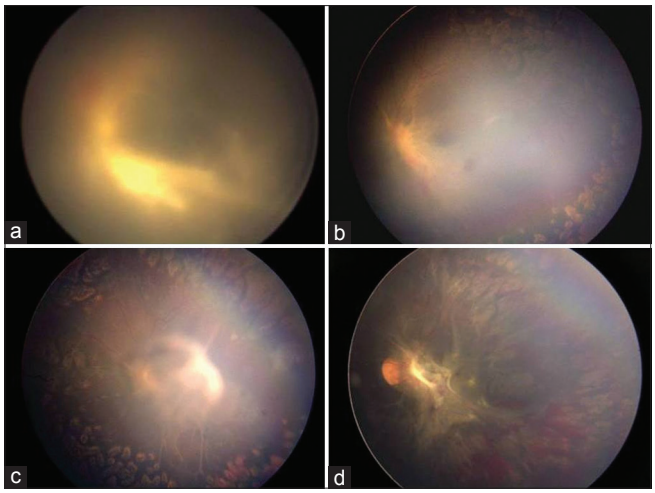

Figure 1: Course of disease in the left eye of an infant with aggressive posterior retinopathy of prematurity who developed infectious endophthalmitis after intravitreal ranibizumab injection. (a) Fundus photograph shows signs of resolving endophthalmitis/vitritis at day 6 after injection (35 weeks). (b) At 42 weeks following laser photocoagulation, media had cleared with resolved neovascularization with minimal central retinal traction. (c) At 48 weeks, retinopathy of prematurity reactivated with severe worsening of central vitreoretinal traction. (d) Post lens-sparing vitrectomy (55 weeks), retinal traction had reduced in height with resolving preretinal hemorrhage and central macular pucker

exercising caution when considering the use of intravitreal anti-VEGFs in infants with ROP. Major studies have not reported any cases of endophthalmitis related to the intraocular injection in ROP.[1,4]

Endophthalmitis in infancy poses many challenges such as lack of obvious clinical features, delayed presentation, difficulty in differentiating between infectious and sterile inflammation, possibility of initial misdiagnosis as metastatic endophthalmitis, and need for multiple examinations under anesthesia.

Endophthalmitis in infancy particularly in ROP should be managed with inpatient treatment. Definite intravitreal and intravenous antibiotic therapy is not known for exogenous endophthalmitis in neonates. However, given the safety profile and outcomes in studies on endogenous endophthalmitis in infants,[5-7] standard empirical intravitreal therapy (preferably a combination of vancomycin with ceftazidime or amikacin) should be given at earliest after taking vitreous tap for culture sensitivity testing. Wang and Xiang used one-third of adult dosage in their case based on the approximation that a premature infant's eye is one-third of the volume of an adult eye.[3] Similar to Ranibizumab dosage, half of the adult dosage was used in our case (0.5 mg vancomycin, 1 mg ceftazidime, and 200 μg dexamethasone).

Intravenous therapy with broad antimicrobial coverage should also be started after taking vitreous sample. Meropenem, amikacin, or piperacillin-tazobactam seem to be the ideal empirical systemic therapy with higher vitreous penetration as per the studies in infants.[5,7] Vitrectomy is usually reserved in cases of endophthalmitis in infants

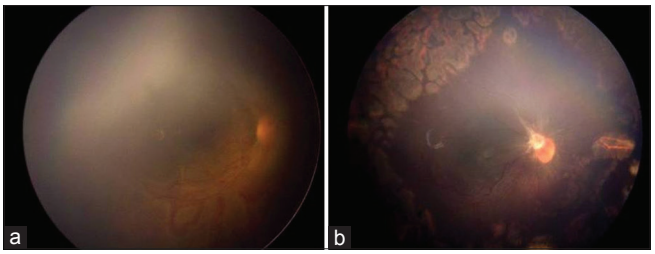

Figure 2: (a) At 37 weeks, the right eye shows zone 1 aggressive posterior retinopathy of prematurity with severe plus disease and avascular loops. (b) At 42 weeks, neovascularization had regressed following complete laser photocoagulation with minimal central retinal traction

because of significantly higher risk of ocular complications and anesthesia-related morbidity and mortality. However, endophthalmitis in ROP warrants early surgery if not responding with medical management.

The presence of endophthalmitis affects the follow-up management of ROP. The media haze due to vitritis/vitreous membranes may hamper visualization of retina making evaluation of plus disease and stage of disease difficult. The response to anti-VEGF therapy cannot be evaluated well in such cases. Furthermore, rescue laser which is often needed as adjuvant treatment in advancing APROP may be difficult to perform.

Late disease reactivation is not uncommon after initial quiescence following intravitreal anti-VEGF injection in ROP.[1,8,9] This usually occurs due to persistent avascular peripheral retina. However, surprisingly in our case, reactivation occurred despite adequate laser, leading to rapidly progressive tractional retinal detachment which necessitated urgent surgery, although the endophthalmitis had resolved well initially. Possibly altered inflammatory milieu due to endophthalmitis may have adversely affected the disease progression.

Conclusion

After injecting anti-VEGF drugs in ROP, close monitoring for signs of endophthalmitis and disease reactivation is essential and such cases should be managed aggressively.

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Conflicts of interest

There are no conflicts of interest.

References

1. Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efficacy of intravitreal bevacizumab for stage 3+retinopathy of prematurity. N Engl J Med 2011;364:603-15.
2. McCannel CA. Meta-analysis of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor agents: Causative organisms and possible prevention strategies. Retina 2011;31:654-61.
3. Wang J, Xiang D. Early clinical characteristics of bacterial endophthalmitis in retinopathy of prematurity after intravitreal

bevacizumab injection: A case report. Exp Ther Med 2017; 13:3563-6.

4. Nicoară SD, Nascutzy C, Cristian C, Irimescu I, Ștefănuț AC, Zaharie G, *et al.* Outcomes and prognostic factors of intravitreal bevacizumab monotherapy in zone I stage 3+ and aggressive posterior retinopathy of prematurity. J Ophthalmol 2015;2015:102582.
5. Basu S, Kumar A, Kapoor K, Bagri NK, Chandra A. Neonatal endogenous endophthalmitis: A report of six cases. Pediatrics 2013;131:e1292-7.
6. Sparks JR, Recchia FM, Weitkamp JH. Endogenous group B streptococcal endophthalmitis in a preterm infant. J Perinatol 2007;27:392-4.
7. Lohrer R, Belohradsky BH. Bacterial endophthalmitis in neonates. Eur J Pediatr 1987;146:354-9.
8. Snyder LL, Garcia-Gonzalez JM, Shapiro MJ, Blair MP. Very late reactivation of retinopathy of prematurity after monotherapy with intravitreal bevacizumab. Ophthalmic Surg Lasers Imaging Retina 2016;47:280-3.
9. Hajrasouliha AR, Garcia-Gonzales JM, Shapiro MJ, Yoon H, Blair MP. Reactivation of retinopathy of prematurity three years after treatment with bevacizumab. Ophthalmic Surg Lasers Imaging Retina 2017;48:255-9.