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Case Report

Unilateral Bevacizumab Injection in Zone 2 Retinopathy of Prematurity

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Abstract

Introduction: Retinopathy of prematurity (ROP) is a retinal vascular developmental disorder and leading cause of infant blindness in developed countries. Laser photocoagulation is well known as gold standard treatment for ROP however, for instants it causes visual fields defects and some refractive errors such as myopia. Anti–vascular endothelial growth factor (antiVEGF) therapy has shown benefits in vascular disease where vascular endothelial growth factor (VEGF) has an important role on the pathophysiology. There are several reports in literature about bilateral antiVegf injection. We report a patient with bilateral beneficial effect after unilateral injection of bevacizumab

Case Description: A premature patient with birth weight of 980 grs and gestational age of 30 weeks with diagnosis of bilateral Zone 2 Retinopathy of prematurity (ROP) and plus disease on right eye. We decided to inject unilateral half of the adult dosage (0,625mg) of bevacizumab at the neonatal intensive care unit (NICU). Potential risks and benefits were explained.

Discussion/Conclusion: Selected cases with plus disease in one eye, unilateral injection of bevacizumab must be considered. It was evidenced by fellow eye effects. Prospective clinical trials are indicated to assess these therapies in order to decrease long-term potential deleterious systemic effects that have not been reported significantly in the literature yet.

Keywords: *Retinopathy of Prematurity; Plus Disease; Vegf; Unilateral antiVegf; Bevacizumab; Laser Photocoagulation*

Retinopathy of prematurity (ROP) is a retinal vascular developmental disorder and leading cause of infant blindness in developed countries [1]. Laser photocoagulation is well known as gold standard treatment for ROP, however, for instants it causes visual fields defects and some refractive errors such as myopia. Anti–vascular endothelial growth factor (antiVEGF) therapy has shown benefits in vascular disease, for example: proliferative diabetes retinopathy, diabetic macular edema, retinal veins occlusions, and choroidal neovascular membrane, where vascular endothelial growth factor (VEGF) has an important role on the pathophysiology of these conditions, there are several reports in literature about bilateral effects of antiVegf injection in patients who have received unilateral injection. Wu Z, Sadda

SR reported a case of bilateral beneficial effect of both unilateral ranibizumab and bevacizumab in a patient with branch retinal vein occlusion [2], Sharma NS., *et al*. Eye (London) (2015). Sir, re: 'Fellow eye effect of unilateral intravitreal bevacizumab injection in eyes with diabetic macular edema' the authors reported improvement in the non-injected eye of patients that received unilateral bevacizumab for diabetic macular edema [3]. A previous study also reported a significant difference in the mean macular thickness of the fellow eye treated with unilateral intravitreal bevacizumab for diabetic macular edema, but no difference in the fellow eye of those receiving unilateral ranibizumab [4]. Vascular endothelial growth factor is a critical molecule that has an important physiological role in the development of premature infants [5]. Off-label use of anti–vascular endothelial growth factor (VEGF) therapy in the form of bevacizumab has been widely used in several vascular diseases including Retinopathy of prematurity (ROP).

Case Description

A premature patient with birth weight of 980 grs and gestational age of 30 weeks. On examination with binocular ophthalmoscopy in anterior segment there is evidence of poorly dilated pupil in both eye and iris rubeosis on right eye. On fundus examination on right eye there is evidence of retinal hemorrhage, supero-temporal, vascular ridge and vascular tortuosity in at least 8 hours of the clock, we classified as a zone 2 ROP with plus disease (Figure 1) on left eye showed vascular tortuosity and nonvascular ridge in two hours of the clock temporal (pre-plus disease). RetCam a digital fiberoptic wide-angle fundus camera was used for documentation, at onset, for follow up and for consultation. Due to critical conditions (neonatal sepsis), laser photocoagulation was deferred. Therefore, unilateral 0,625 mg of intravitreal bevacizumab injection was scheduled at the neonatal intensive care unit (NICU), right eye was selected by the surgeon due to evidence of plus disease.

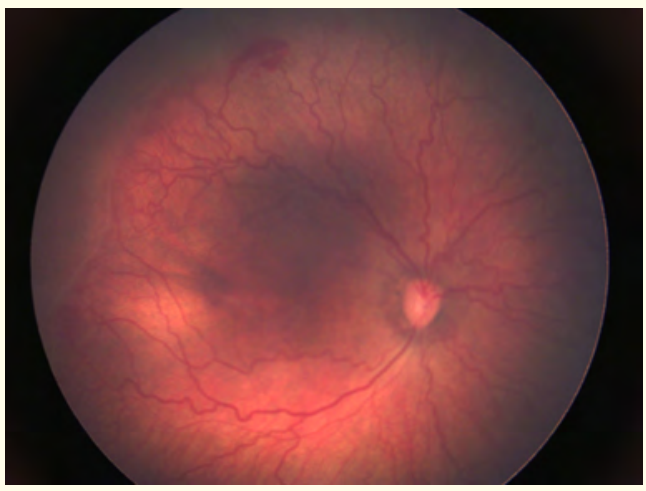

Figure 1A: *(OD) right eye fundus showing retinal hemorrhage at 11 hours, vascular ridge and vascular tortuosity. (Zone 2 ROP with plus disease).*

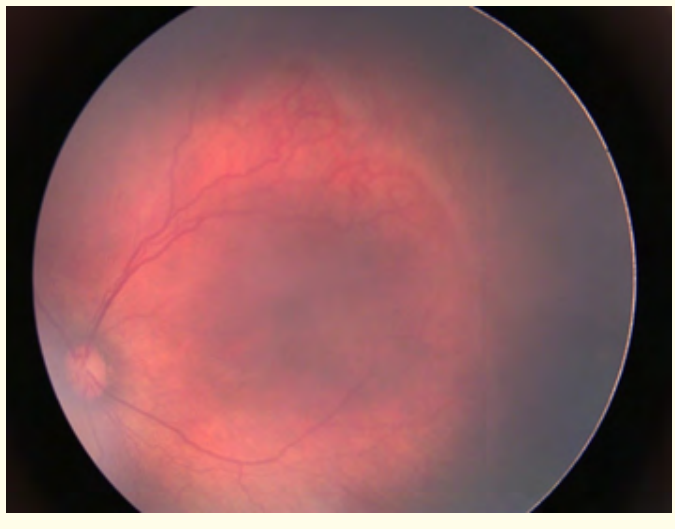

Figure 1B: *(OS) left eye fundus shows zone 2 ROP with no vascular ridge and vascular tortuosity in at least 2 hours of the clock (pre plus disease).*

Two days after injection, there was evidence of regression of vascular activity in both eye (Figure 2), and one week after treatment avascular zone remain in zone 2 (Figure 3). Follow up was planned weekly the first month and every two weeks from the second month after injection, at ten weeks of follow up, vascular activity did not reappeared even on untreated eye (left eye). Bilateral laser photocoagulation was planned in order to avoid reactivation of the vascular activity, with complete regression of the disease (Figure 4).

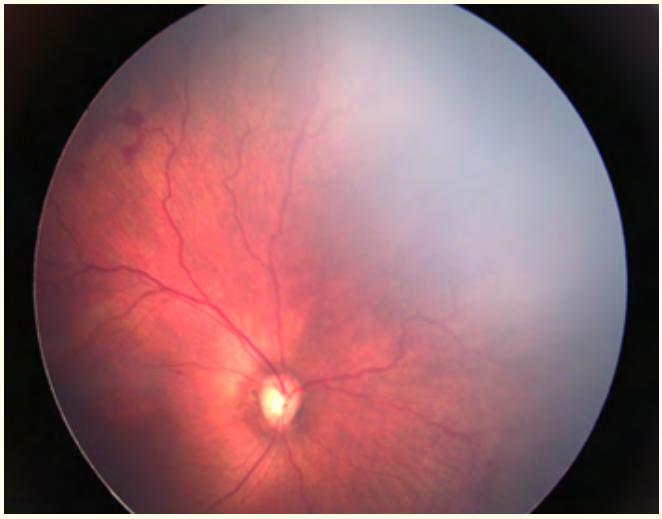

Figure 2A: *(OD) pole posterior image shows mild regression of the retinal hemorrhage and plus disease 48 hours after bevacizumab injection.*

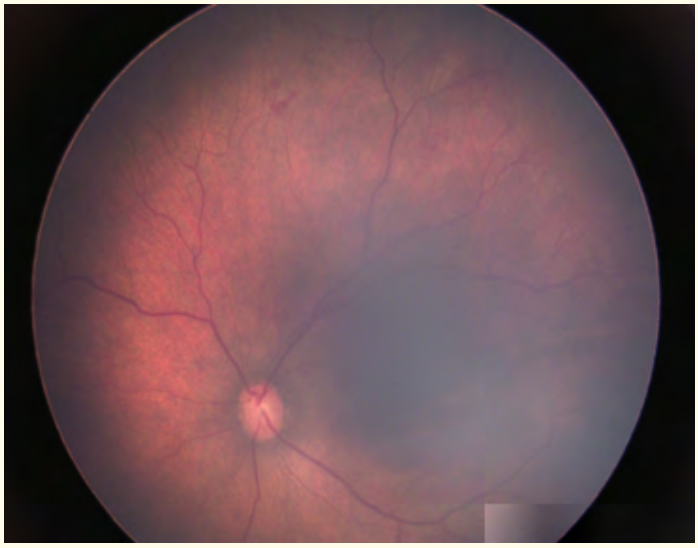

Figure 2B: *(OS) fellow eye shows regression of the pre- plus disease 48 hours despite not having received treatment.*

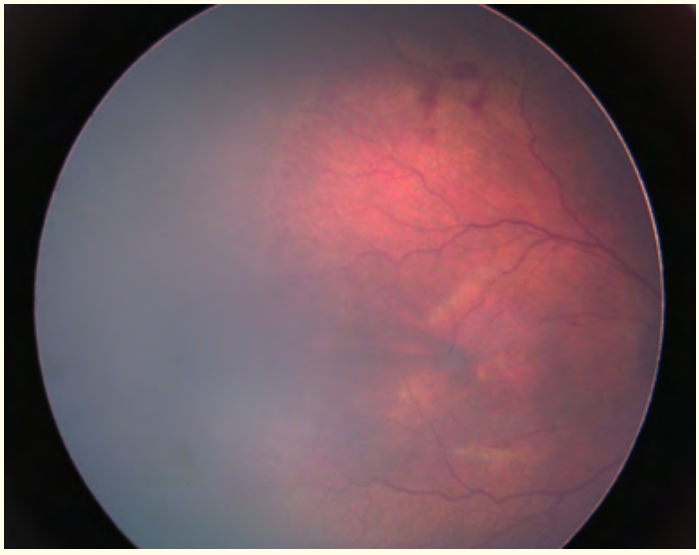

Figure 3A: *(OD) one week after treatment, stabilization of the bridge, no plus disease, avascular retina remains in zone 2.*

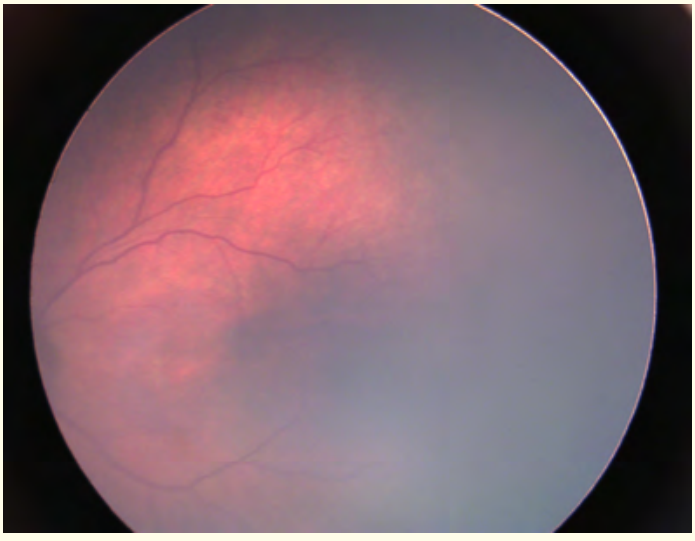

Figure 3B: *(OS) one week after treatment, regression of pre plus disease with stabilization of the ridge, avascular retina remains in zone 2.*

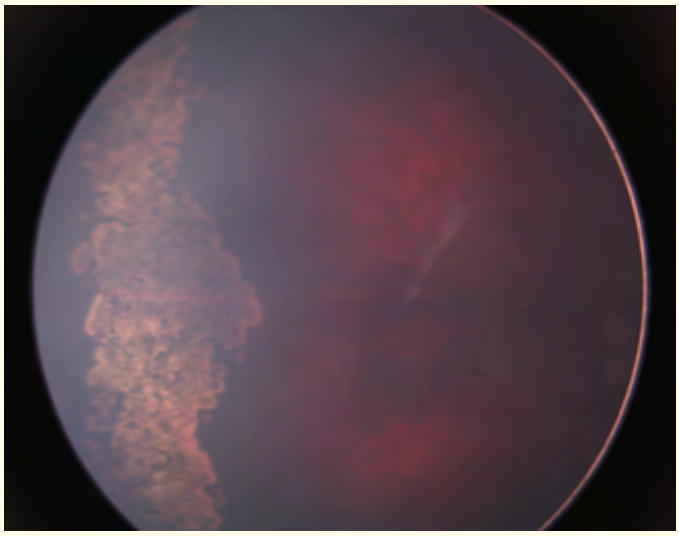

Figure 4A: *OD right eye with completed regression two weeks after laser photocoagulation.*

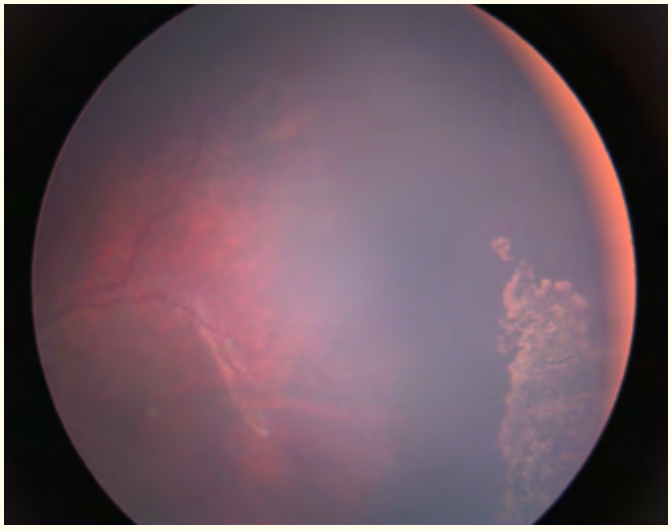

Figure 4B: *Left eye (no treated eye) peripheral retina shows laser scars in zone 3 and completed regression of the disease.*

Discussion

Anti-vegf therapy has been very helpful in ROP. There are several reports about the effects of bilateral injection of bevacizumab but just a few about bilateral effect of unilateral bevacizumab injection in ROP. Cagatay Karaca., *et al*. [5] reported a short series of four patients that showed reduced vascular activity in the untreated eye after unilateral injection of bevacizumab by systemic route and just one

patient of the series developed tractional retina detachment in the injected eye. All untreated eye did received laser as second procedure with complete regression of the disease. According with our knowledge this is the largest series reported in the literature of unilateral bevacizumab in ROP [5].

In our patient of very low weight premature baby with local and systemic relative limitations to perform laser photocoagulation at the operating room (OR), such as: neonatal sepsis, poorly dilated pupils, and the evidence of plus disease in the right eye. Unilateral half of the adult dosage of anti–vascular endothelial growth factor injection was decided to do at the neonatal intensive care unit (NICU) following the same OR protocol, an inform consent was previously signed by the parents, potential risks and benefits were explained by the neonatologist and ophthalmologist. Surgeon selected the right eye (OD) because of the presence of plus disease. There are studies that support the use of bilateral or unilateral half of the adult dosage (0,625 mg) of bevacizumab; however, the ideal dose, adverse effects, and effect on mortality rates remain undetermined [6] authors have thought that the bevacizumab was not capable to penetrate the intact retina. Sato., *et al*. [7] showed a significant increase in serum bevacizumab levels after unilateral and bilateral intravitreal injection. Serum VEGF levels also decreased accordingly.

Routinely we do bilateral injection of ranibizumab as primary or combined treatment for zone 1 or posterior zone 2 ROP [8], but in selected cases like ours (with plus disease just in one eye), unilateral injection of bevacizumab was considered the best option because it get into bloodstream and reduce Vegf more than ranibizumab, it was evidenced by fellow eye effects.

Weeks after injection due to persistent avascular retina in zone 3, we decided to planned bilateral laser photocoagulation with complete regression of the disease.

We strongly believe that avascular retina with not treatment for instant could represent a risk of reactivation of the vascular activity after injection of bevacizumab, unlike occurs in ranibizumab patients where most of them complete vascularization of the retina after injection in zone 2 ROP with no need of laser photocoagulation.

In conclusion, prospective clinical trials are indicated to assess these therapies in order to decrease long-term potential deleterious systemic effects that have not been reported significantly in the literature yet.

Discussion/Conclusion

Selected cases with plus disease in one eye, unilateral injection of bevacizumab must be considered. It was evidenced by fellow eye effects. Prospective clinical trials are indicated to assess these therapies in order to decrease long-term potential deleterious systemic effects that have not been reported significantly in the literature yet.

Conflict of Interest Disclosures

None of the authors have financial interest.

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