CASE REPORT

Very Late Reactivation of Retinopathy of Prematurity After Monotherapy With Intravitreal Bevacizumab

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Abstract

The authors report a case of very late reactivation of retinopathy of prematurity (ROP) after bevacizumab monotherapy. A female born at 630 g and 24 weeks received two bilateral treatment of bevacizumab (Avastin; Genentech, South San Francisco, CA) for aggressive posterior ROP (APROP). At 2.5 years of age, ROP reactivated in the form of tractional retinal detachment in one eye and milder reactivation in the other. Although intravitreal bevacizumab treatment is effective in inducing regression of ROP, late reactivation and retinal detachments can occur after initial extended quiescence. Due to alterations of disease progression after bevacizumab, close follow-up by peripheral fluorescein angiography and laser ablation of persistent avascular retina is recommended to prevent disease reactivation and progression to retinal detachment.

[*Ophthalmic Surg Lasers Imaging Retina*. 2016;47:280–283.]

Introduction

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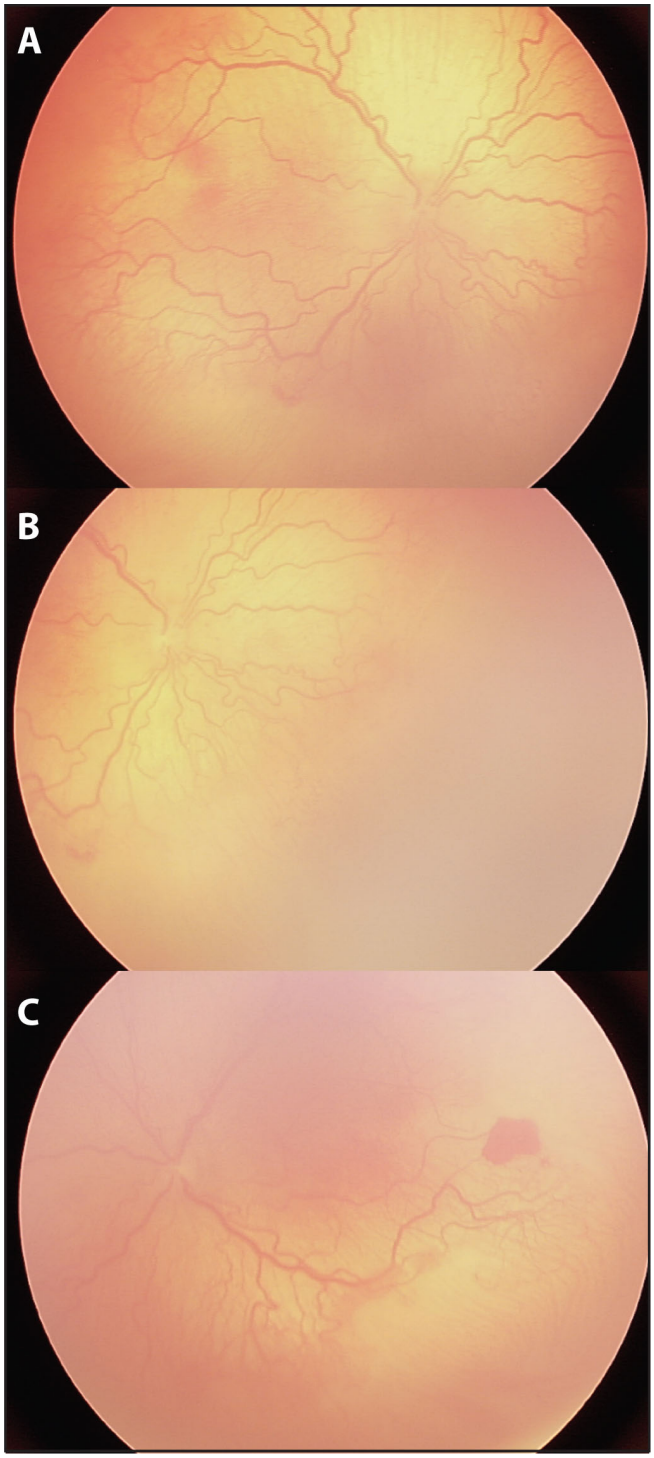
A female infant, born at 630 g and 24 weeks PMA, developed zone 1 aggressive posterior retinopathy of prematurity (APROP) with plus disease at 34 weeks PMA (Figure 1) and was treated with bilateral intravitreal injection of bevacizumab (0.625 mg). The patient was examined every 1 to 2 weeks with significant regression of ROP, including resolution of plus disease and further vascularization into zone 2. At 51 weeks PMA, she had reactivation of ROP (zone 2, stage 3 with plus disease). The mother declined laser treatment at this point, due to need for sedation, and preferred another injection of intravitreal bevacizumab (0.625 mg) due to the ease of administration. The mother was informed that ROP could reactivate at some point in the future, and the authors recommended laser treatment within the next few months to prevent future reactivation. The family transferred care to another hospital system and therefore began seeing another retinal specialist, who was familiar with ROP screening and treatment. The patient was seen on several occasions, the last of which was at 80 weeks PMA, at which time there was no recurrence of ROP, peripheral vascularization was deemed adequate based on ophthalmoscopy, and no further treatment was performed.

Figure 1.

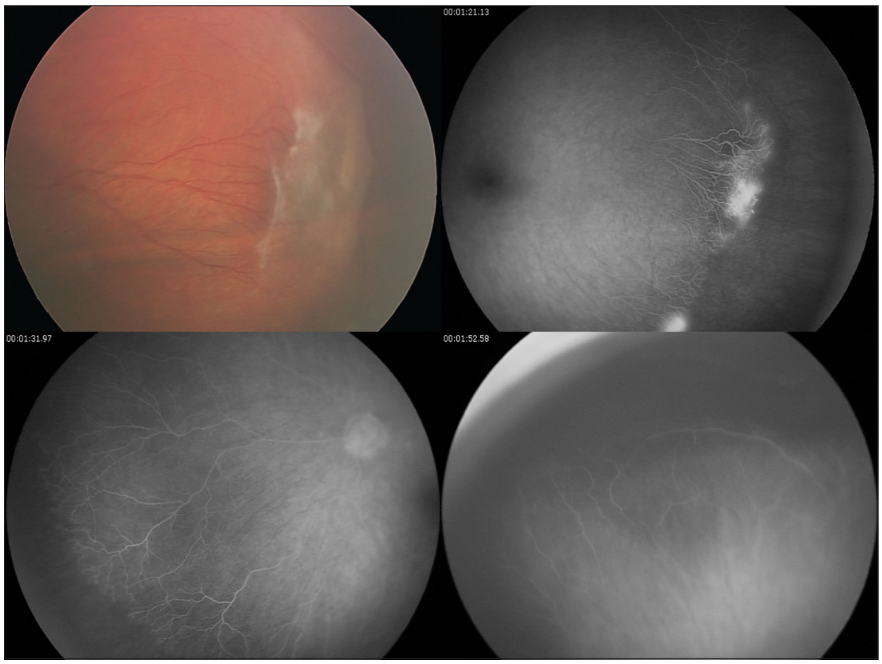


Aggressive posterior retinopathy of prematurity in both eyes. (A) Right eye: note tortuosity. (B) Right eye: note zone 1 termination. (C) Left eye: note fine neovascular blush inferiorly.

The patient was sent to pediatric ophthalmology for further follow-up.

At 2.5 years of age, the patient developed a vitreous hemorrhage and a retinal detachment and was referred to our service for repair. Exam under anesthesia revealed a dense vitreous hemorrhage in the right eye with visible vascular extra retinal proliferation (EFP). The left eye demonstrated vascularization in zone 2 with anterior EFP temporally. Fluorescein angiogram of the same eye confirmed vascular termination past the area of original ROP with late leakage at its boarder (Figure 2). Peripheral nonperfusion was noted in all four quadrants. Ultrasound of the right eye demonstrated tractional retinal detachment (Figure 3).

Intraoperatively subretinal exudate was present. The retinal detachment in the right eye has been repaired after two vitrectomies, and the left eye has remained stable after peripheral laser photocoagulation.



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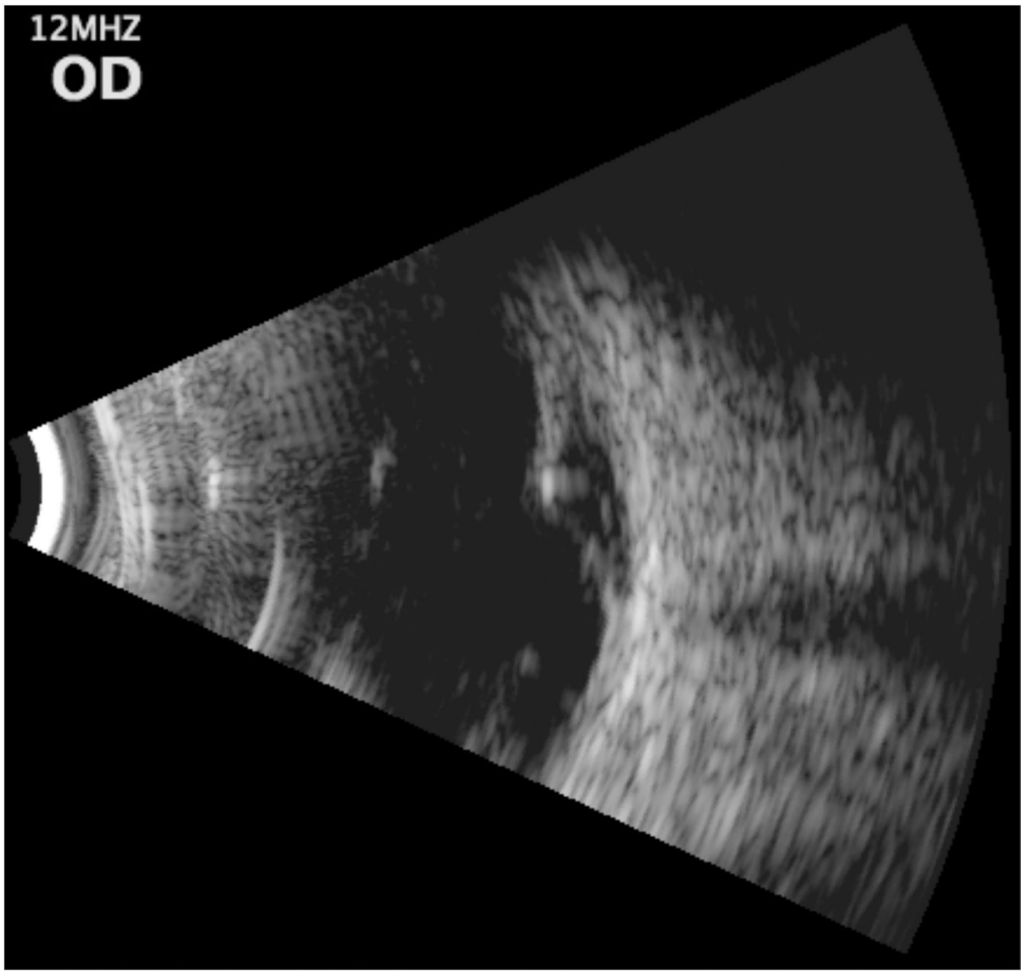

Figure 3.
Ultrasound of the right eye at 2.5 years of age. Tractional retinal detachment is present temporally.

Discussion

In recent years after the publication of the BEAT-ROP study, multiple cases have been published highlighting a late reactivation of ROP post-bevacizumab, leading to tractional retinal detachment and poor visual outcome.[2–4] In the original BEAT-ROP publication, no detachments were present at up to 54 weeks.[1] In a recent publication of 2.5 year follow-up from the BEAT ROP study, no eyes that received bevacizumab were noted to have had retinal detachment, although two eyes needed vitrectomy for media opacity.[5] Another recently published large study regarding bevacizumab-treated ROP from Turkey found no late recurrences and had a mean follow-up of approximately 90 weeks PMA.[6] However, the average birthweight was relatively high (1 kg), so applicability of those results to other smaller neonates is uncertain. Considering those publications, the rate of late ROP reactivation related retinal detachment after bevacizumab is likely small but may increase with age, as persistent peripheral avascular retina may continue produce low levels of vascular endothelial growth factor (VEGF) that may build up over time. The use of bevacizumab has been linked to an alteration in disease time course after treatment, which differs in form from the disease process after laser therapy. In the BEAT-ROP study, the mean (standard deviation [SD]) time to recurrence in infants with zone 1 ROP was 19.2 (SD = 8.6) weeks for patients treated with bevacizumab compared to 6.4 (SD = 6.7) weeks in those treated with laser.[1] Even with 2.5-year follow-up in the recent BEAT-ROP publication, it is possible that the study was not long enough to be able to capture instances of very late recurrence of ROP.[5] That study may also be underpowered to detect infrequent late reactivation. However infrequent late reactivation may be, the visual consequences may be severe.

Laser therapy permanently destroys the avascular retina and thus halts the future production of VEGF, which is the likely trigger of late reactivation in ROP. In eyes treated with bevacizumab, incompletely vascularized peripheral retina may still produce low levels of VEGF long after the effects of initial bevacizumab injections have worn off. Subsequent, slow accumulation of VEGF may lead to late reactivation of ROP. Thus, it has been our practice to follow infants who receive bevacizumab injections closely and then to perform fluorescein angiography and laser photocoagulation to persistent avascular retina at 60 weeks PMA. This patient's care was transferred and she was followed until 80 weeks by another retinal specialist, who did not think laser treatment was indicated. To our knowledge, no recurrence after 80 weeks has been reported prior to this case.

Given the devastating consequences of recurrent ROP, we encourage prolonged and frequent follow-up for patients who have received bevacizumab injections. As patients grow, the ability to examine the peripheral retina to identify persistent avascular retina becomes more difficult, and fluorescein angiography should be considered. We believe that untreated avascular retina, which remains in many post–bevacizumab-treated ROP eyes, may lead to progressive disease similar to familial exudative vitreoretinopathy, in that there is risk of exudate, extraretinal neovascularization, tractional element formation, and retinal detachment.[4] We believe, therefore, that post-bevacizumab ROP eyes are at risk of chronic, life-long disease and need to

be followed long-term. Additional studies are needed to determine which patients are at risk for late recurrence. Until that has been determined, it is imperative that practitioners remain vigilant for late reactivation so it can be treated promptly. The alternative, which we strongly recommend, would be planned laser to persistent avascular retina identified by fluorescein angiography.

We suspect even later reactivation may occur, in the coming years or even decades, in some patients who have not had laser.

References

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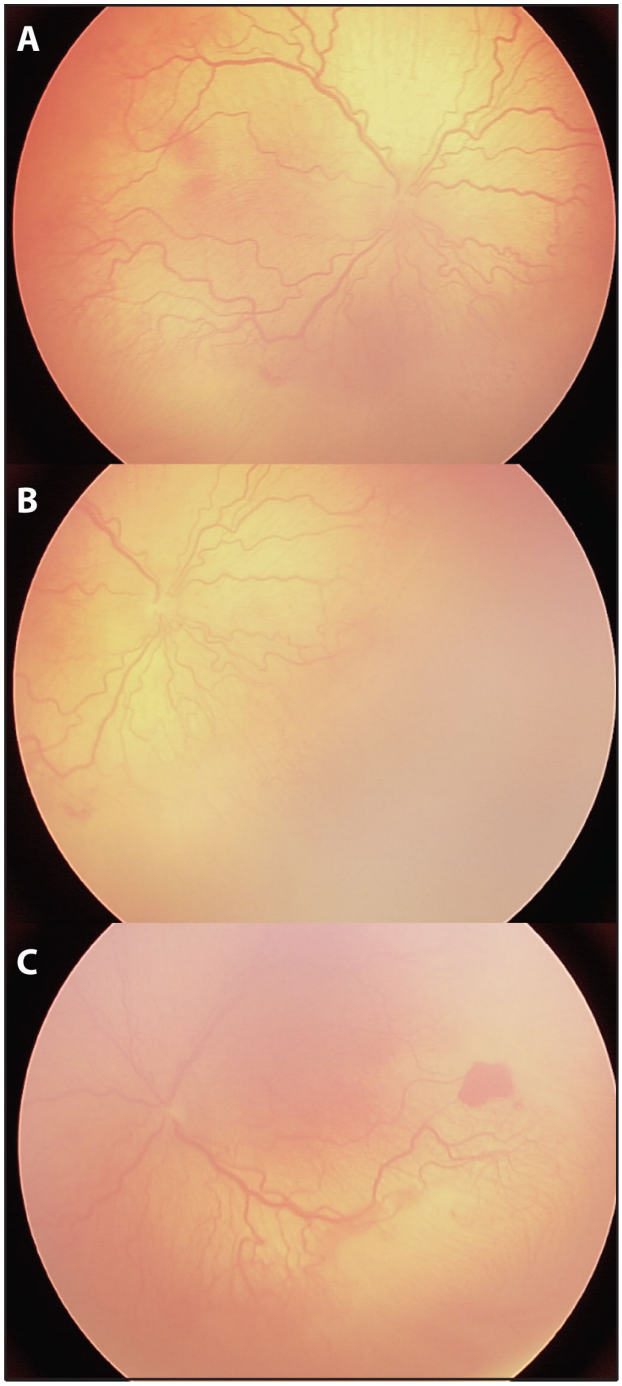

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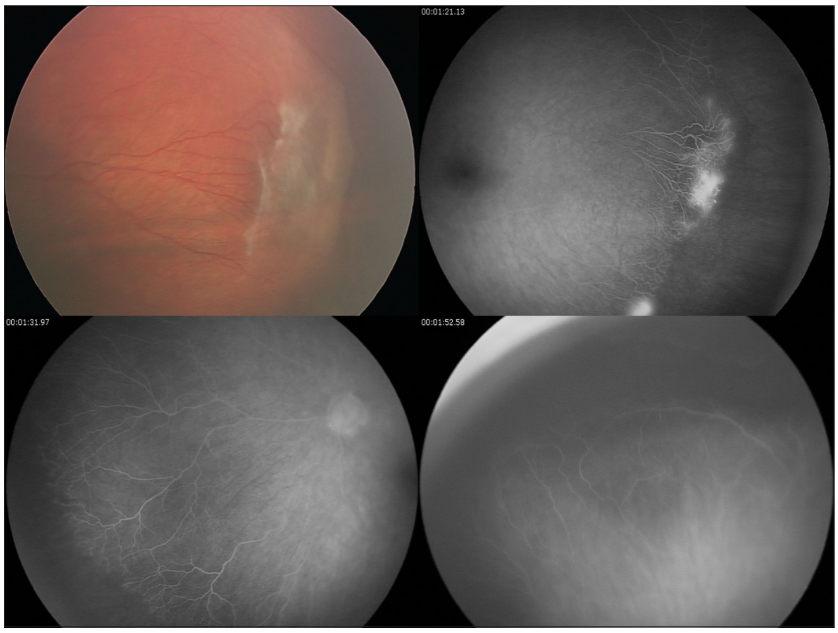

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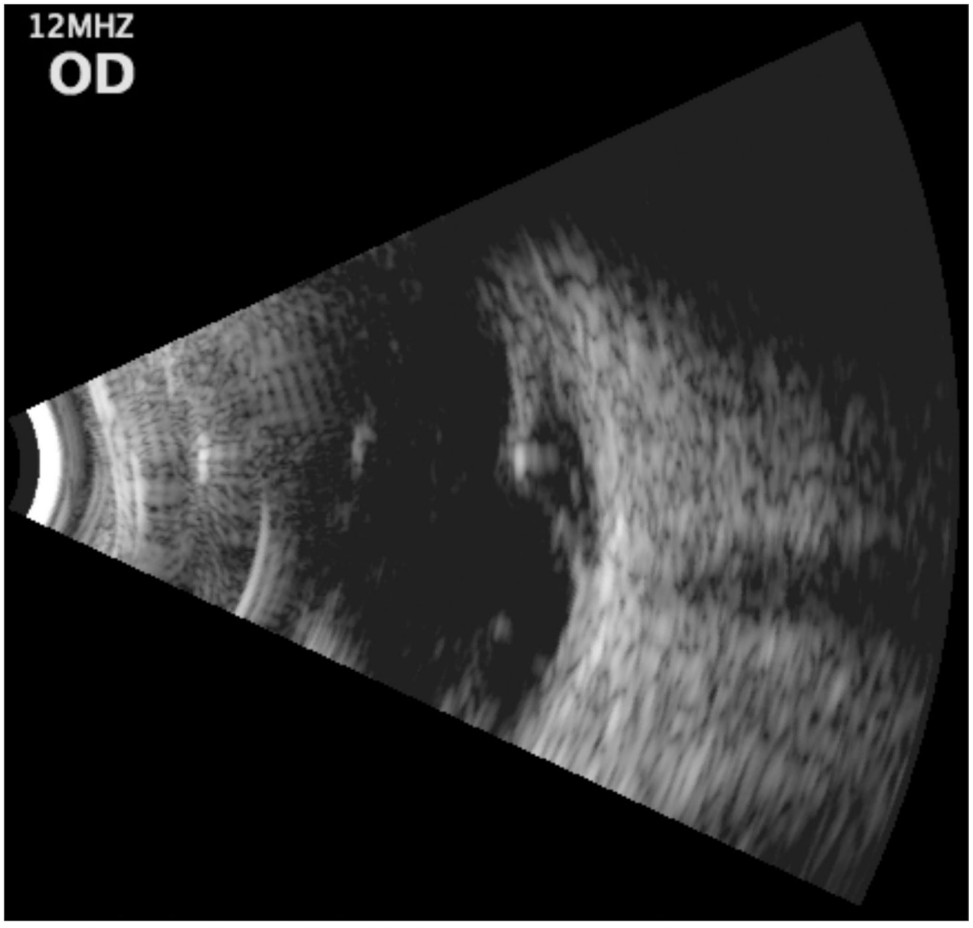

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