

Exudative retinopathy and detachment: A late reactivation of retinopathy of prematurity after intravitreal bevacizumab

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A 25-week postmenstrual age premature infant was treated with bilateral intravitreal bevacizumab for retinopathy of prematurity at 35 weeks' PMA. Postinjection, the retinal vessels progressed anteriorly within the retina. The patient presented 1 year after injection with bilateral exudative retinal detachments. The right eye was treated with intravitreal bevacizumab, laser ablation, and scleral buckling, resulting in resolution of the exudation and detachment. The left eye was treated with vitrectomy and lensectomy, but persistent exudation and detachment remained. This case demonstrates the rare complication of exudative retinal detachment in the setting of retinopathy of prematurity, which may become more common with increasing use of bevacizumab. Importantly, it also demonstrates the need not only for frequent examination after bevacizumab injection for retinopathy of prematurity but long-term follow-up as well, until either the retina is fully vascularized or peripheral ablation is performed.



A premature infant of 25 weeks' postmenstrual age was treated with bilateral intravitreal bevacizumab for retinopathy of prematurity (ROP) at 35 weeks' postmenstrual age. After injection, the retinopathy resolved and the retinal vessels progressed anteriorly within the retina. The patient presented 1 year after injection with bilateral exudative retinal detachments. The right eye was treated with intravitreal bevacizumab, laser ablation, and scleral buckling, resulting in resolution of the exudation and detachment. The left eye was treated with vitrectomy and lensectomy, but exudation and retinal detachment persisted. This case demonstrates the need for frequent examination after bevacizumab injection for ROP as well as long-term follow-up.

ROP is a disease of vascular development that in severe cases causes extraretinal fibrovascular proliferation and subsequent tractional retinal detachment. The use of bevacizumab for posterior ROP has gained evidence-based support from BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity), a randomized, controlled trial.¹ However, blockage of vascular

endothelial growth factor (VEGF) has been associated with significant changes in the chronology of vascular growth and reactivation patterns of ROP.²⁻⁴ Safe use of this new intervention requires awareness of altered disease patterns. We present an unusual aspect to the disease pattern after bevacizumab injection for ROP—Coats-like exudative retinopathy.

Case Report

A 415 g female infant, born at 25 weeks' postmenstrual age, developed type 1 prethreshold ROP (zone 1, stage 3, moderate plus disease) and received bilateral, intravitreal injections of bevacizumab (0.625 mg/0.025 mL) at 35 weeks' postmenstrual age. The treating physicians chose bevacizumab because of the clinical impression of a more favorable response of posterior disease to anti-VEGF treatment. History revealed no prenatal complications or any family history of ocular conditions.

The following week the retinopathy regressed, with disappearance of plus disease and extraretinal fibrovascular proliferation. Biweekly examination of the patient during the next 4 months revealed progressive anterior growth of retinal vessels. The examination interval was extended to 6 months. Examination at 81 weeks' postmenstrual age showed retinal detachment in both eyes, and the patient was referred to Retina Consultants, Des Plaines, Illinois, for treatment. Examination under anesthesia with fundus photography and fluorescein angiography (RetCam Clarity Medical, Pleasanton, CA) showed scattered microaneurysms, dilated and telangiectatic vessels, mild posterior exudate, extensive peripheral exudate, anterior avascular retina, anterior extraretinal fibrovascular proliferation, and tractional retinal detachment in the right eye (Figures 1 and 2). Treatment with bevacizumab injection to decrease presumed VEGF-mediated vascular permeability, laser ablation of the avascular retina, and scleral buckle to support the peripheral tractional elements resulted in resolution of exudate and detachment in the right eye (Figure 3). The left retina has been partially reattached with vitrectomy and lensectomy, but significant peripheral tractional elements and posterior exudate have persisted (e-Supplement 1, available at jaapos.org).

Discussion

This case of severe exudative retinopathy in ROP occurred at a markedly earlier age than previously reported cases.⁵⁻⁷

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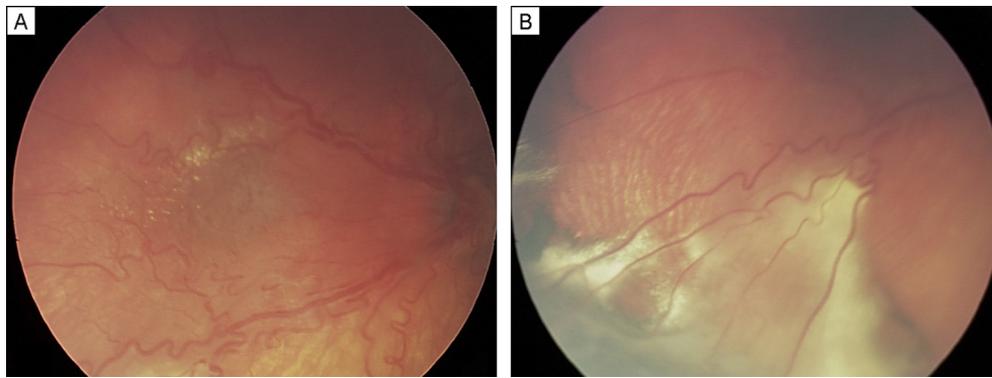


FIG 1. Fundus photographs of the right eye taken at 82 weeks' postmenstrual age, 46 weeks after the injection of bevacizumab, demonstrating tortuous, dilated vessels with discrete areas of exudation (A) and large, wedge-shaped area of subretinal exudation (B).

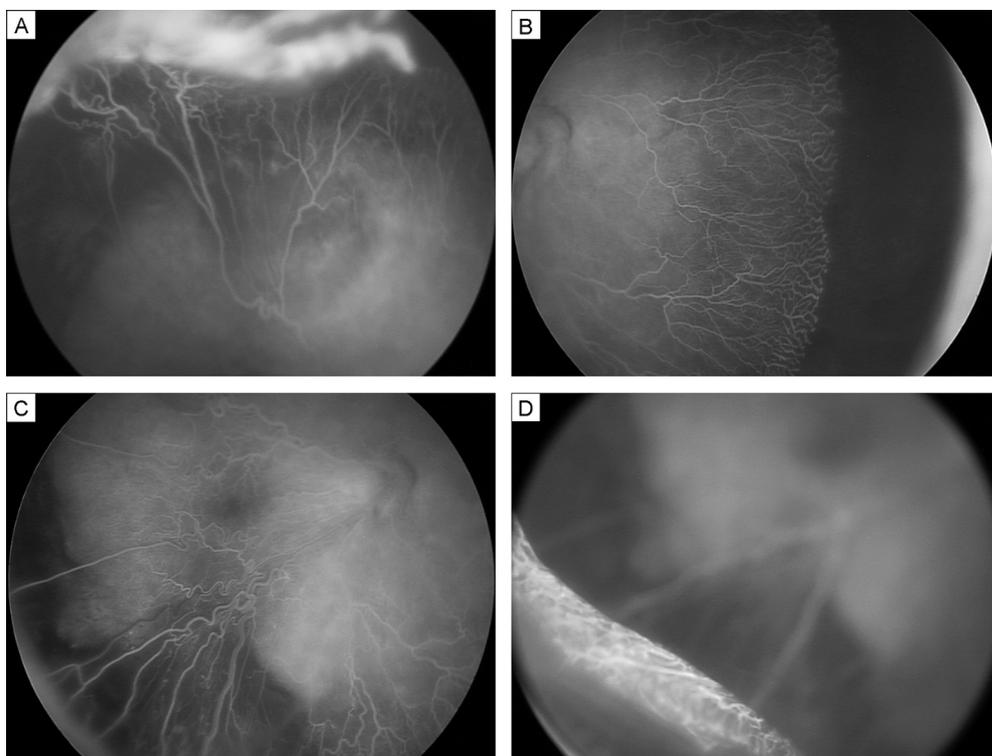


FIG 2. Fluorescein angiogram of the right eye taken at 82 weeks' postmenstrual age, 46 weeks after the injection of bevacizumab, demonstrating telangiectatic vessels and leakage from fibrovascular proliferation superiorly (A), brush border vascular termini nasally (B), microaneurysms with wedge-shaped hypofluorescence caused by exudation (C), and a peripheral anterior rim of avascular retina (D).

The periphery of right eye showed features common to Coats disease and familial exudative vitreoretinopathy: telangiectatic vessels, microaneurysms, large areas of avascular retina, vascular termini with a brush-like appearance, and extensive lipid exudate extending from the equator to the periphery. The left eye showed severe tractional retinal detachment but had extensive exudate as well. Exudative retinopathy has been described in small case series as a rare complication in adults with a history of ROP but without peripheral ablation.⁵⁻⁷ This form of exudative retinopathy is distinct from Coats disease by history and the presence of macular heterotopia and peripheral

traction, features commonly seen in familial exudative vitreoretinopathy. Exudative retinal detachment can occur in posterior uveitic diseases and acutely after peripheral retinal ablation for ROP.^{8,9} However, exudative retinal detachment in these instances is not associated with massive lipid exudate, microaneurysms, or telangiectasis.

We believe that similar to those diseases, peripheral avascular retina in our patient as well as in those cases described by Brown and colleagues⁵ and Tasman^{6,7} induces the exudative retinopathy. We suspect that incompletely or abnormally vascularized peripheral retina beyond

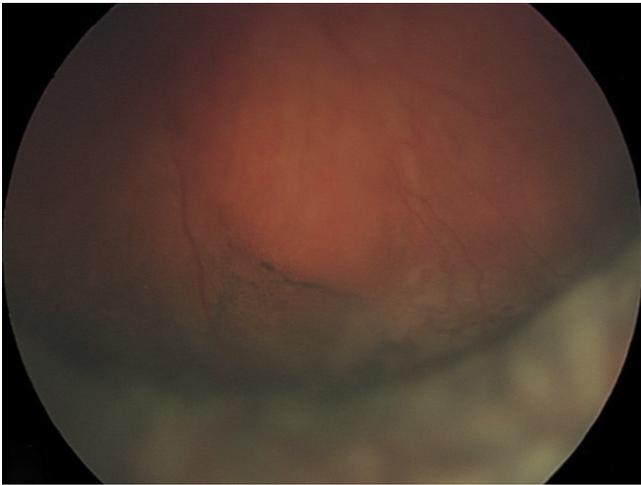


FIG 3. Fundus photograph of the right eye 13 weeks after injection of bevacizumab, peripheral laser treatment, and scleral buckle placement showing resolution of exudates and detachment inferiorly, leaving pigment mottling.

60 weeks' postmenstrual age may produce low levels of VEGF. Long-term mild-to-moderate elevation of VEGF may produce increased retinal vascular permeability, microaneurysms, and telangiectatic vessels, with or without late extraretinal fibrovascular proliferation. Clearly this exudative retinopathy as a late sequelae of ROP is rare, given its scarcity when considering the number of untreated children with ROP who never develop such disease. However, the timing of these sequelae may be altered significantly after treatment of acute-phase ROP with bevacizumab.

Eyes that had aggressive posterior ROP requiring bevacizumab may still have relatively large areas of avascular peripheral retina producing VEGF, even after the retinal vessels have grown anteriorly after treatment. We view this late exudative sequelae to be attributable to reaccumulation of VEGF and thus treatable in a way similar to most VEGF-mediated diseases, namely, with anti-VEGF injection and ablation of poorly or nonperfused retina. Clearly, this speculation does not account for the full complexity of the ROP response after bevacizumab, because it likely involves other growth factors and environmental and genetic elements. In any event, this present case serves as a reminder that new biologic interventions change the intraocular milieu in fundamental ways that may produce complex effects.

Our findings, in combination with those of previous reports, suggest that infants treated with bevacizumab should be followed closely and long term, with special attention to a larger variety of findings not described in the

limited sample size and follow-up period covered by the BEAT-ROP study.^{2-4,10} We are concerned in particular about long-term consequences, over years and decades, of peripheral avascular retina left after bevacizumab treatment. Furthermore, we suggest consideration of peripheral ablation as an alternative to frequent long-term follow-up. Unfortunately, the long-term disease behavior of eyes that would have received peripheral ablation in the recent past is simply unknown. Some untreated eyes, from the years before ablation became common, did progress late to exudative retinopathy; however, the rarity of this retinopathy cannot be extrapolated to the current ROP population, due to the sizeable downward shift in birth weight and gestational age.

Literature Search

PubMed was searched (1967-2012) in February 2012 using the following terms: *retinopathy of prematurity exudates* and *retinopathy of prematurity exudative retinal detachment*. The reference sections of relevant articles were also reviewed. Untranslated foreign articles were excluded.

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