Fluorescein Angiography of Recurrent Retinopathy of Prematurity After Initial Intravitreous Bevacizumab Treatment

Standard treatment for type 1 prethreshold retinopathy of prematurity (ROP) is laser ablation.1 A number of recent reports describe regression of ROP with intravitreous injection of the anti–vascular endothelial growth factor (VEGF) agent bevacizumab.2–6 We describe a premature boy diagnosed with type 1 prethreshold ROP who received bilateral intravitreous bevacizumab injections and demonstrated initial resolution. Two months later, clinical examination and fluorescein angiography demonstrated a circumferential vascular anastomotic pattern at the location of the initial stage 3 complex with radial vessels that continued peripherally toward a second, more anterior stage 3 complex. This was then successfully treated with laser photocoagulation.

Report of a Case. A 26-week-gestation boy weighing 675 g at birth and with multiple medical problems was transferred to our institution for treatment of presumed type 1 prethreshold ROP in the setting of prominent tunica vasculosa lentis. Although initial examination disclosed immature vessels in zone 2, he quickly progressed to stage 3 with plus disease by age 34 weeks. Given the patient’s critically ill health, the neonatology service recommended against prolonged sedation for laser therapy. Therefore, after an informed discussion with his parents, light intravenous sedation was administered to the infant and his eyelashes and conjunctival surfaces were prepared with 10% povidone-iodine topical solution. Intravitreous injections of bevacizumab (0.75 mg/0.025 mL) were administered bilaterally using a separate, sterile eyelid speculum for each eye. The infant was examined on postinjection day 1 and then weekly for 2 months. Within 2 weeks, examination identified regression of the lens-associated vessels, disappearance of extraretinal fibrovascular proliferation, and marked regression of plus disease. Subsequently, radial vessels grew anteriorly within the retina.

Two months after treatment, a second stage 3 complex developed anterior to the original stage 3 complex that had regressed, leaving a circumferential vascular anastomosis (Figure 1). Fluorescein angiography demonstrated anterior extraretinal fibrovascular proliferation with leakage and a more posterior circumferential vascular ring with associated telangiectasis but without leakage (Figure 2). Because the patient had become systemically stable enough for adequate sedation, conventional peripheral laser photocoagulation was administered to both eyes. Subsequent examination demonstrated bilateral cicatricial changes of the stage 3 complex over the next 3 weeks, with stabilization by 1 month after laser treatment without further vascular changes on follow-up.

Comment. Evidence indicates that ROP may be a biphasic disease with an initial oxygen-induced vascular obliteration phase, followed by hypoxia-induced vessel proliferation.7 Anti-VEGF therapy may be effective in the second phase8 and as a single dose because there is theoretically only 1 burst of VEGF.9 This is in contrast to other ocular neovascular conditions, such as age-related macular degeneration and diabetic retinopathy, where aberrant VEGF production often recurs as a result of longstanding disease.

Supporting this, Mintz-Hittner and Kuffel3 reported that a single bilateral injection of bevacizumab in 22 eyes of 11 infants induced regression of acute ROP and allowed vascularization of the peripheral retina to resume. In contrast, another report1 described a 41-week-old boy with zone 1, stage 2 plus disease that initially responded to bevacizumab treatment, but recurrence developed 11 weeks later. This recurrence responded to a second bevacizumab injection, but the patient died soon afterward of systemic illness.

In our case, zone 2, stage 3 plus disease treated on day 64 of life responded markedly to intravitreous bevaciz-
umab, but 2 months later a second, more anterior stage 3 complex developed. Although the occurrence of multiple ridges is well documented, it is a rare event compared with other patterns of ROP regression. To our knowledge, this is the first angiographic documentation of circumferential anastomosis at the bevacizumab-induced regression site with radial vessels progressing anteriorly to form a second stage 3 complex. The time course seems to indicate quiescence due to bevacizumab followed by reactivation from its waning effect. Although this case provides further evidence of the efficacy of bevacizumab as a treatment option for patients with ROP when laser treatment is not feasible, it also emphasizes that the angiogenic stimulus potentiating the sight-threatening complications of ROP may recur or persist after a single injection of an anti-VEGF agent. This case also provides further support that intravitreal bevacizumab does not necessarily inhibit subsequent retinal vascular development.¹

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Support for TGFB1 as a Susceptibility Gene for High Myopia in Individuals of Chinese Descent

Zha et al¹ reported a haplotype-tagging single-nucleotide polymorphism (SNP) (rs4803455) within the transforming growth factor β1 (TGFB1 [OMIM 190180]) gene and observed evidence of association between it and severe myopia (spherical equivalent [SE] ≤ −8.0 diopters [D]) using a case-control sample of Chinese individuals (N = 600; P < .001). They also provided evidence of replication for a previously reported neighboring SNP (rs1800470) in moderate linkage disequilibrium with rs4803455.² For both SNPs, the minor allele was at decreased risk for high myopia and their effect was strongest within a model of recessive inheritance. Exhustive analysis by Zha and colleagues showed the best correlate for high myopia susceptibility within TGFB1 to be rs4803455. We thus sought to assess this association within Chinese children in the Singapore Cohort Study for Risk Factors in Myopia.

Methods. The Singapore Cohort Study for Risk Factors in Myopia cohort has been previously described.³⁴ The students enrolled in the study are examined annually, and serial eye measurements are taken using standardized protocols. These include cycloplegic refraction and axial length measurement of the eyeball. To remove ethnicity as a potential source of population heterogeneity, we only included children of Chinese descent in this genotyping exercise (n = 978). Phenotypic classification of the children into those with severe myopia, those with nonevere myopia, and nonmyopic controls was made at visit 4 when the children were aged 10 to 12 years. The SE was defined as sphere plus half-negative cylinder. High myopia was defined as an SE of −5.0 D or less; mild to moderate myopia was defined as an SE between −5.0 D and −0.5 D; and nonmyopic controls included those with an SE greater than −0.5 D. The axial length of the globe was measured by contact ultrasound A-scan biometry as previously described.³⁴ The SNP rs4803455 was analyzed in an opportunistic but hypothesis-driven manner as the data were available from an ongoing genome-wide association study using the Illumina HumanHap 550 Beadchips (Illumina, Inc, San Diego, California; http://www.illumina.com). Rigorous quality-control steps were performed, including genotype success rate, missingness, population stratification, departure from Hardy-Weinberg equilibrium in controls, monomorphism, excess heterozygosity, cryptic relatedness, and sex discrepancy. Data analysis was performed using SPSS version 17 statistical software (SPSS Inc, Chicago, Illinois). Pairwise linkage disequilibrium between markers was computed based on the squared Pearson correlation coefficient (r²) using the overall data set. We used the linkage disequilibrium information to select a set of 4000 independent autosomal markers (r² < 0.16) with approximately equal intermarker distance (approximately 670 kilobases [kb]) across the genome. This set of markers was used to examine sample relationships with the Graphical Representation of Relationships program (Cen-