CORRESPONDENCE

Late-onset tractional fibrovascular proliferation post–intravitreal bevacizumab following treatment of retinopathy of prematurity

We report the case of a premature infant born at 24 weeks postmenstrual age (PMA) with a birth weight of 652 g who was treated with intravitreal bevacizumab (IVB) in both eyes for zone 1, stage 3 retinopathy of prematurity (ROP) with plus disease. At 63 weeks PMA, he was treated successfully with repeat IVB injection in the right eye for recurrent vascular proliferation. At 92 weeks PMA, the right eye showed late recurrence of tractional fibrovascular proliferation (FVP) temporally, with no leakage, retinal detachment, macular ectopia, or disc dragging. Barrier laser photocoagulation was performed in the right eye to prevent sight-threatening tractional retinal detachment (TRD) and macular dragging.

A Caucasian male born at 24 weeks PMA with a birth weight of 652 g was screened for ROP in the neonatal intensive care unit. At 38 weeks PMA, indirect ophthalmic examination revealed stage 3 ROP in zone 1 with plus disease in both eyes. The patient's parents elected for treatment with IVB injection over laser photocoagulation, which was administered (0.75 mg in 0.03 mL) in both eyes under sedation. The infant was followed weekly and then bi-weekly until 55 weeks PMA, with examination at that time consistent with regressed stage 3 retinopathy without plus disease. At 63 weeks PMA, a single 3–4 clock hours of active FVP was noted in the right eye temporally, which showed leakage on fluorescein angiography (FA) (Fig. 1). The parents again elected for IVB, which was repeated in the right eye. At 68 weeks PMA, under anaesthesia, examination and FA was performed, which showed regressed vascular proliferation in the right eye with retinal vessels in zone 2 and persistent peripheral avascular retina in both eyes in all quadrants (Fig. 2A, B). The patient returned for follow-up examination 6 months later at 92 weeks PMA (15 months chronological age) with recurrent tractional FVP temporally in the right eye (Fig. 2C). FA revealed fibrous proliferation with localized peripheral retinal traction. No peripheral retinal detachment, macular ectopia, or disc dragging was noted (Fig. 2D). Barrier laser photocoagulation was applied around the peripheral fibrous proliferation extending to ora in the right eye (Fig. 2E). Both eyes continued to show retinal vessels in zone 2 with peripheral avascular retina in all quadrants. No laser photocoagulation was done to the avascular retina in either eye.

Currently, large published clinical studies[1–4] have reported incidence of early recurrences of stage 3 and stage 4/stage 5 ROP post-IVB monotherapy at up to 1 year of age. In the initial BEAT-ROP study,[1] IVB monotherapy as compared with conventional laser therapy was noted to be significantly beneficial in treating stage 3 ROP with plus disease in zone 1. The post-IVB recurrence rate was noted to be 4% (6 eyes) as compared with 22% (32 eyes) in the laser-treated group. Of the 6 eyes with recurrence, 1 eye displayed evidence of macular dragging and 2 eyes developed retinal detachments. Hu et al[2] later reported recurrent stage 3 ROP post-IVB monotherapy in 17 eyes of 9 patients at ages ranging from 49 to 69 weeks PMA, of which 5 eyes had recurrence in the form of retinal detachment. The authors reported that all 17 eyes at the initial treatment had elevated extraretinal vessels (EFP) with plus disease. The presence of pretreatment elevated EFP in itself will predispose the eye to high risk for TRD.

In a recent study following up on the results of the BEAT-ROP group,[3] the incidence of stage 3 ROP recurrence post-treatment with IVB monotherapy was found to be 8.3% for treated infants, with average early recurrence occurring within 10 weeks after injection (mean 51.2 weeks PMA). Two of 20 infants (10%) demonstrated recurrence at 57.9 and 64.9 weeks PMA. The authors also reported 3 eyes of 2 infants with stage 4 or stage 5 ROP with no comments on the age at which the late complications were noted. Another retrospective case series[4] described retinal detachment in 23 infants with ROP, in whom 25 of 35 eyes were treated with IVB monotherapy, and only 4 eyes received 2 IVB injections. Of the 35 eyes, 25 eyes had either previous or subsequent laser photocoagulation with IVB. The study reported early progressive retinal detachment at a mean of 70 days (range 4–335 days) postinjection occurring at a mean age of 35 weeks PMA. This study reported the earliest TRD at approximately 1 week postinjection, with the latest TRD reported at 82 weeks PMA postinjection. The authors proposed that upregulation of TGF-β profibrotic cytokine promotes TRD when an infant is close to term.[4] In another large study[5] using primarily IVB monotherapy, the authors reported 253 injections, of which 11 were second and 4 were third injections. The study followed infants for a mean of 90 weeks (range 82–105 weeks) PMA, with no retinal detachments and completely matured retinal vasculature in all 122 infants. The studies show distinct variability among practices in the treatment pattern for type 1/APROP, with some practices using primarily IVB monotherapy and others supplementing laser photocoagulation by 60–70 weeks PMA post-IVB.

Our case describes recurrence of late-onset tractional proliferation postregression of stage 3 ROP with 2 IVB injections in 1 eye. The pattern of regression of stage 3 ROP in our case did not differ from that described in the literature. There are only 2 cases reported in the literature[6,7] with very late onset of TRD, macular ectopia, and poor visual outcome beyond 1 year of chronological age, both by the same group of physicians. Both cases are described with late onset of TRD, macular ectopia, and disc dragging at 2.5 and 3 years of chronological age post-treatment with IVB monotherapy. One of the babies had

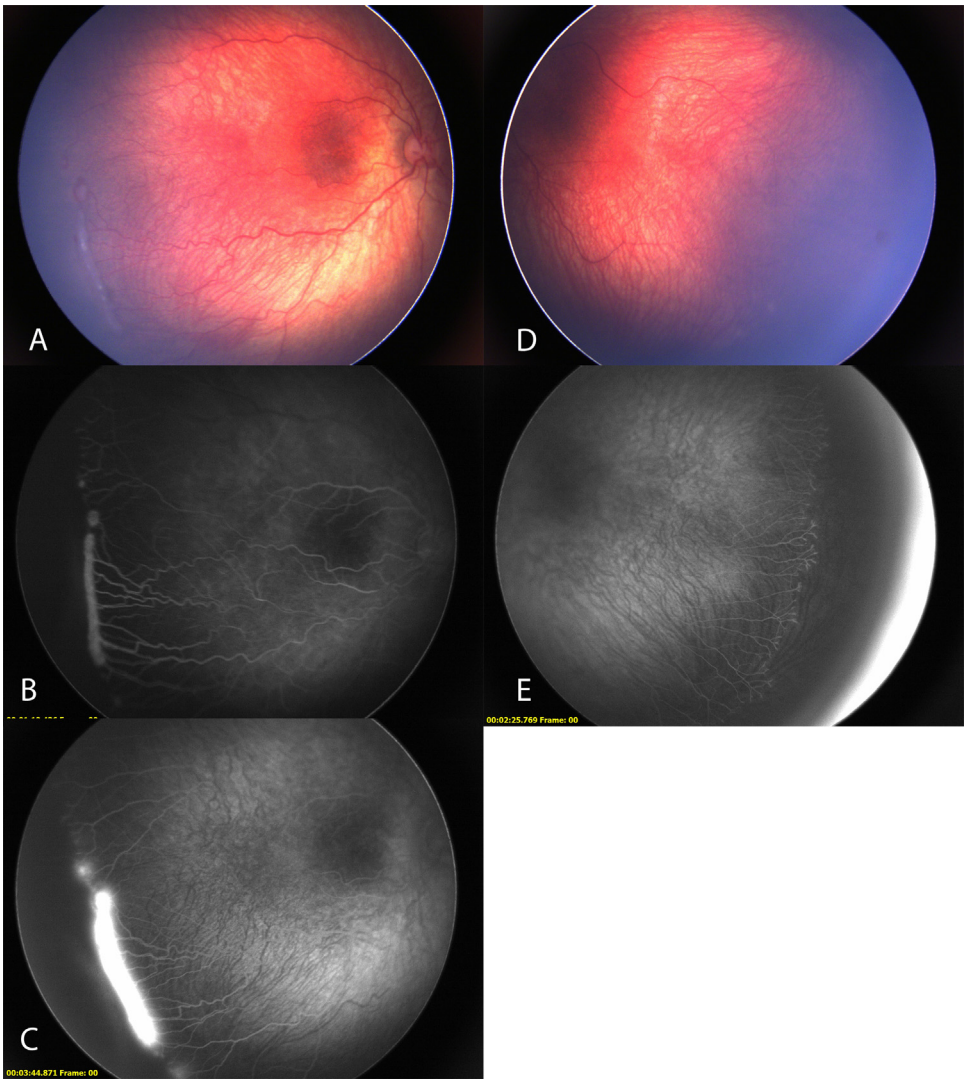

Fig. 1—Fundus pictures of the 24-week premature infant with a birth weight of 652 g treated with intravitreal bevacizumab in both eyes for zone 1, stage 3 retinopathy of prematurity at 38 weeks postmenstrual age (PMA). (A) Colour fundus photograph of the right eye with recurrence of stage 3 fibrovascular proliferation along the temporal vascular–avascular junction seen at 63 weeks PMA (9 months chronological age). (B) Fluorescein angiography (FA) of the right eye in arteriovenous phase showing hyperfluorescent leaking from the fibrovascular proliferation (FVP) along the temporal vascular–avascular junction with retinal vessels in zone 2. Peripheral avascular retina can be seen temporally. (C) Fluorescein angiography of the right eye in the late phase showing hyperfluorescent leakage from the FVP along the temporal vascular–avascular junction. (D, E) Colour fundus photograph and FA of the left eye with a small hemorrhage seen along the temporal vascular–avascular junction with peripheral avascular retina. The FA shows the clear termination of temporal retinal vessels with persistence of peripheral avascular retina. The left eye retinal vessels were seen in zone 2.

recurrent stage 3 ROP at 51 weeks PMA and was retreated with repeat second IVB. The authors have not provided the fundus or FA images before or after repeat IVB injections. Both cases were followed post–IVB monotherapy until 80 and 75 weeks PMA, respectively, by ophthalmoscopy and later were sent to physicians outside their group for follow-up eye examinations. No record of examination under anaesthesia or FA was performed until the babies were seen at 2.5 and 3 years of age with sight-threatening late TRDs in both eyes. The study also refers to the presence of leakage on FA in both eyes, with the authors proposing that every infant treated with IVB should undergo FA and subsequent laser photocoagulation to the avascular retina.[6,7] A third case with bilateral exudative retinal detachment post–IVB monotherapy was reported by the same authors. A similarity between the third case and the previous 2 cases is that all were seen in the eye clinic without depressed retinal examinations until seen with retinal detachments.[8]

Our patient, after the second IVB treatment at 63 weeks PMA for recurrent FVP in the right eye, showed regression of FVP at the follow-up examination under anaesthesia at 68 weeks PMA. FA showed complete regression of proliferation with diffuse hyperfluorescent staining along the regressed FVP and persistent avascular retina in all quadrants. The infant was seen 6 months later