Delayed-onset retinal detachment after an intravitreal injection of ranibizumab for zone 1 plus retinopathy of prematurity

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Intravitreal injection of bevacizumab has been shown to satisfactorily treat retinopathy of prematurity; nevertheless, the safety of antivascular endothelial growth factor therapy in children remains uncertain. We report a patient with bilateral, zone 1, stage 3 plus retinopathy of prematurity who was treated with combined laser photocoagulation and intravitreal ranibizumab injection and demonstrated full regression at 3 months after injection but then developed bilateral retinal detachments 1 month later.

Case Report

A boy of 32 weeks' gestational age weighing 1,690 g at birth was referred to our department for retinopathy of prematurity (ROP) screening at 36 weeks. Having been treated with nasal continuous positive airway pressure for 2 days and 20% oxygen for 8 days, he presented with zone 1, stage 3 ROP with plus disease in both eyes and premacular hemorrhage in the right eye, with extraretinal fibrovascular proliferation extending more than180° (Figure 1A, B). Fluorescein angiography revealed leaking, tortuous vessels restricted to zone 1 and avascular peripheral retina elsewhere (Figure 1C, D).

After a discussion with the parents about the results of conventional laser photocoagulation and intravitreal anti-vascular endothelial growth factor (VEGF) injection, it was decided that treatment would combine intravitreal injection of ranibizumab with laser photocoagulation. Both eyes were treated with dense laser photocoagulation to the peripheral avascular retina (300 mW, OD: 2,297 applications, OS: 2,369 applications) by the use of a laser indirect ophthalmoscope (Visulas 532s; Carl Zeiss, Jena, Germany). Immediately after laser photocoagulation, 0.30 mg (0.03 mL) of ranibizumab (Lucentis; Genentech, Inc, South San Francisco, CA) was injected with a 30-gauge needle, which was placed perpendicularly 1 mm behind the limbus to prevent lens injury. Three weeks later, premacular hemorrhage of the right eye and extraretinal fibrovascular proliferation of both eyes had almost disappeared. Three months after injection, fundus examination and fluorescein angiography showed flat retinas and slightly attenuated but normal vasculature without extraretinal fibrovascular proliferation in both eyes (Figure 2).

One month later, however, the parents noted that the boy was occasionally unable to make eye contact. Examination of his left eye showed total retinal detachment. At this time the right eye was normal. Two weeks later, the right eye also showed total retinal detachment (Figure 3). Vitrectomy was recommended. The family decided to transfer the baby's care to another hospital, and follow-up was not possible.

Discussion

Most advanced ROP cases treated with anti-VEGF agents have been reported to have favorable results.[1-5] However, Honda and colleagues[6] reported acute contraction of the patient's proliferative membrane beginning 1 day after injection and progressing for 7 days. The authors believed this was similar to the tractional retinal detachment observed in proliferative diabetic retinopathy after bevacizumab injection and thought it might be to the result of a rapid neovascular involution with accelerated fibrosis in response to decreased levels of VEGF. In the present case, total retinal detachments in both eyes occurred after injection of ranibizumab; however, the time from injection to retinal detachment was over the course of 4 months. It is difficult to explain why retinal detachments occurred after the ROP had demonstrated near full regression of extraretinal fibrovascular proliferation 3 months after injection combined with laser. We hypothesize that some extraretinal fibrovascular proliferation regressed incompletely and slowly developed into a tractional complex, leading to retinal detachment. Mintz-Hittner[7] emphasized the importance of timing the intravitreal injections of bevacizumab in treating ROP. She pointed out that when the membrane is extensive, the injection can cause it to contract, leading to retinal detachment. She further noted that the decision to treat with injection of bevacizumab is more complicated in advanced (stage 3 and 4) ROP.

There are numerous potential complications of intravitreal anti-VEGF injection in pediatric patients. Infants may be more vulnerable to VEGF blockade.[8] Infection and trauma can result from the procedure. Furthermore, the full effect of anti-VEGF on normal developing vessels is unknown. Systemic side effects of anti-VEGF antibody are also a concern, although no systemic complications have been reported to date. We used ranibizumab instead of bevacizumab on the basis of the results of the MARINA (Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular

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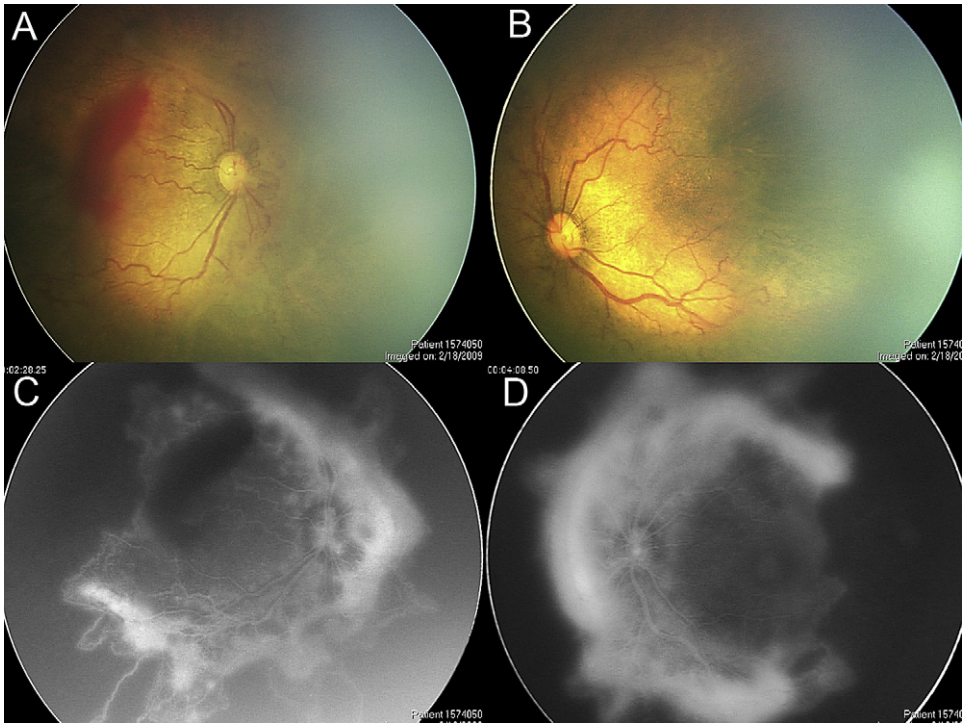

FIG 1. Fundus photographs of the right (A) and left (B) eyes showing, on the right, premacular hemorrhage and extraretinal fibrovascular proliferation around the disk and, on the left, extraretinal fibrovascular proliferation around the disk. Fluorescein angiographs of the right (C) and left (D) eyes showing leaking vessels restricted to zone 1, just temporal to macula and nasal to disk.

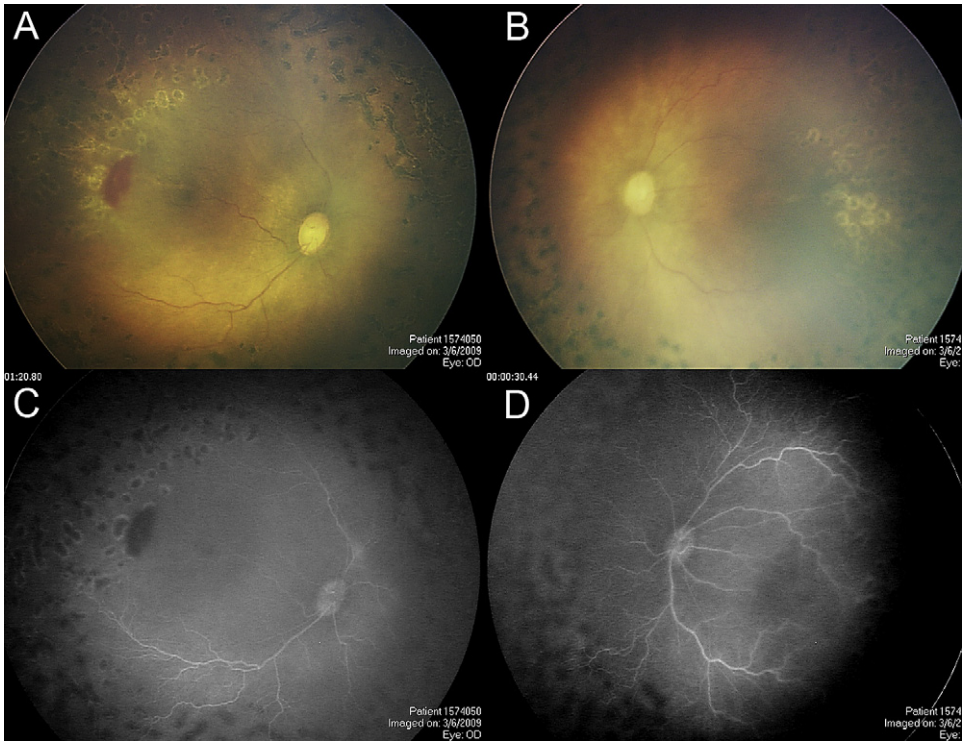

FIG 2. Fundus photographs and fluorescein angiographs of the right (A, C) and left (B, D) eyes 3 months after laser photocoagulation and intravitreal injection of ranibizumab showing regression of extraretinal fibrovascular proliferation and absence of vascular leakage, with normal configuration of the remnant vessels.

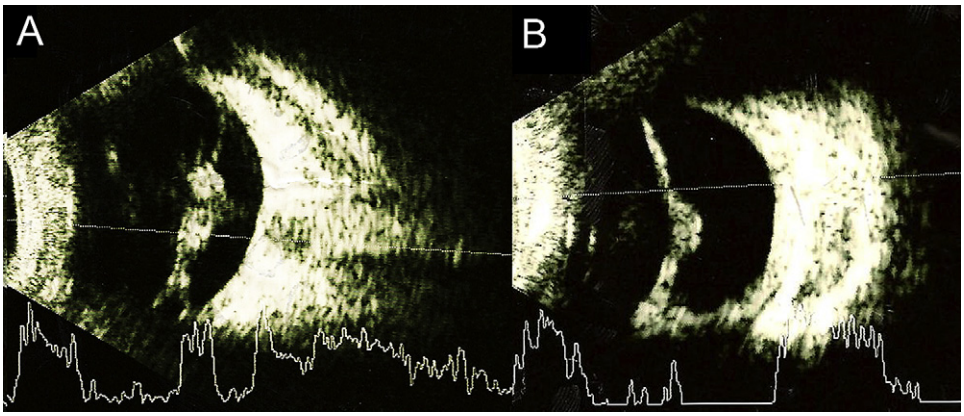

FIG 3. Ultrasonographs of the right (A) and left (B) eyes showing delayed-onset total retinal detachment at 4 months after photocoagulation and intravitreal ranibizumab injection.

Age-Related Macular Degeneration) study,[9] which showed no difference between the treated and control group with regard to systemic complications during 2 years of follow-up. No systemic side effects were identified in our patient.

Of note in our case was the progression of ROP in such a relatively large infant. Reporting on 5 infants diagnosed with stage 3 ROP after birth weights of over 1,500 g, Mandal and colleagues[10] concluded that other factors may contribute to the development of ROP in addition to birth weight and gestational age. In our case, initial examination revealed no abnormalities apart from mild hypoglycemia and hyperbilirubinemia, which were easily treated successfully. There was no evidence of other perinatal factors, such as hyponatremia and intraventricular hemorrhage, no history of blood transfusion, and no indication of retinal dysplasia, familial exudative vitreoretinopathy, or Norrie disease. We were unable to perform genetic analysis because the parents refused to provide consent.

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