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CASE REPORT

Acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab for advanced retinopathy of prematurity

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Abstract
Background Despite the recent reports describing the benefits of the intravitreal injection of bevacizumab (IVB) to treat ocular neovascular disorders, including retinopathy of prematurity (ROP), the possible adverse effects of this therapy must also be described. We report here a case of advanced ROP which showed an acute contraction of the proliferative membrane after an intravitreal injection of bevacizumab.
Methods A female infant born at 23 weeks of gestation with a birth weight of 598 g was referred to the ophthalmologist at 4 weeks of age. With funduscopic examinations, broad avascular retinas were found in both eyes. Since the ROP had progressed to stage 3, zone 1 with plus disease in both eyes, retinal photocoagulation was performed at 10 weeks of age. Despite the adequate photocoagulation therapy, the proliferation progressed further, and partial tractional retinal detachment (TRD) occurred in the right eye, classified as stage 4A with plus disease. After extensive discussion with the parents about the risks and benefits of IVB as an alternative therapy, they consented to the treatment. Under general anesthesia, an intravitreal injection of 0.4 mg bevacizumab was performed at 14 weeks of age.
Results The following day, the vascular component of the fibrovascular membrane (FVM) regressed, and acute fibrosis occurred. However, the ring-shaped FVM contracted centripetally, which caused a deterioration of the TRD. The contraction of the FVM progressed until 7 days after IVB, and resulted in a funnel-like retinal detachment at the posterior retina. The other eye also showed TRD at 19 weeks of age classified as stage 4B, which necessitated a vitrectomy. No systemic complications were noted before and after the treatment.
Conclusions IVB is a useful therapy to maintain aggressive ROP. However, IVB might cause TRD progression in some specific cases.

Keywords Retinopathy of prematurity · Bevacizumab · Complications

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Introduction

Retinopathy of prematurity (ROP) is a serious disorder in premature infants. Although most cases are resolved spontaneously, some cases show acute progression of the fibrovascular proliferation to tractional retinal detachment (TRD) regardless of ordinal retinal photocoagulation therapy, which results in a poor visual prognosis [1]. Recent reports have described the intravitreal administration of bevacizumab (Avastin®, Genetech, Inc, South San Francisco, CA, USA), a humanized anti-vascular endothelial growth factor (VEGF) antibody, to treat ocular neovascular disorders including ROP [2, 3]. Although quite a few adverse events after the intravitreal injection of bevacizumab have been described to date, a deterioration of TRD associated with intravitreal bevacizumab has been reported only in cases of severe proliferative diabetic retinopathy (PDR) [5]. Since ROP shows similar clinical and pathological features as PDR, the same risks of intravitreal bevacizumab may exist. We report here a case

which showed an acute contraction of the proliferative membrane leading to TRD progression after an intravitreal injection of bevacizumab for advanced ROP.

Materials and methods

A female infant was born at 23 weeks of gestation with a birth weight of 598 g. The first ophthalmic examination was performed at 4 weeks of age, and a broad avascular area was found (the vascular area was within Zone 1). Since the ROP had progressed to stage 3, zone 1 with plus disease in both eyes, retinal photocoagulation was performed at 10 weeks of age. The conditions of the photocoagulation were: irradiation time 400 ms, laser power 400 mW, 1330 shots for the right eye and 1276 shots for the left eye, using a GYC-1000 instrument (NIDEK, Osaka, Japan). Despite the adequate photocoagulation therapy, the proliferation progressed further, and partial TRD occurred in the right eye, classified as stage 4A with plus disease (Fig. 1a) [4]. After extensive discussion with the parents about the risks and benefits of surgical treatment versus intravitreal bevacizumab as an alternative therapy, they consented to the treatment with bevacizumab. Under general anesthesia, an intravitreal injection of 0.4 mg bevacizumab was performed at 14 weeks of age.

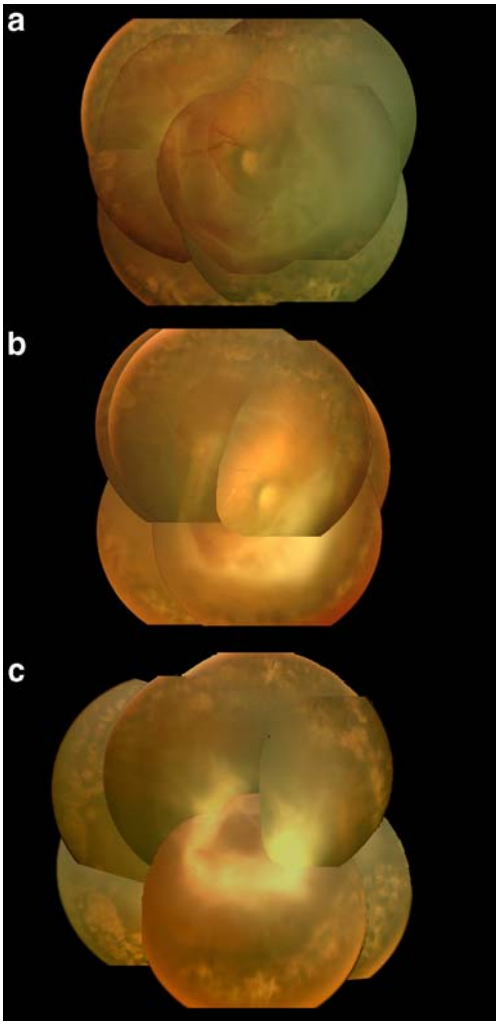

Fig. 1 Fundus photographs. **a** The right fundus before intravitreal bevacizumab shows severe proliferation and partial TRD at the posterior pole. **b** The same fundus the following day after IVB. The FVM fibrosis progressed with a centripetal contraction. **c** The same fundus at 1 week post-intravitreal bevacizumab shows remarkable fibrosis and contraction of the FVM

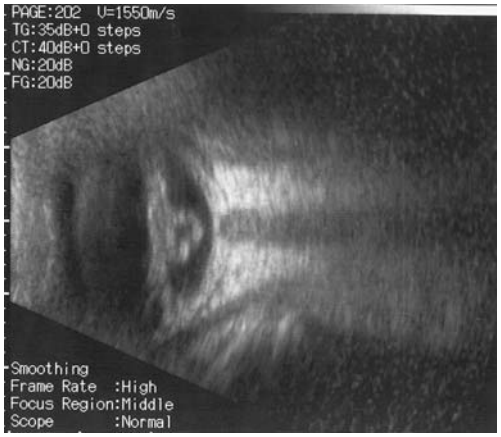

Fig. 2 B-mode ultrasonographic image of the right eye at 1 week after the intravitreal injection of bevacizumab. A funnel-like retinal detachment is present at the posterior retina

Results

The following day, the vascular component of the fibrovascular membrane (FVM) regressed, and the appearance of FVM became fibrotic. However, the ring-shaped FVM contracted centripetally, which caused a deterioration of the TRD. The contraction of the FVM progressed until 7 days after bevacizumab injection, and resulted in a funnel-like retinal detachment at the posterior retina (Fig. 2). Although further treatment was not expected by her parents, the retinal state remained unchanged for more than 6 months. The left eye also showed TRD at 19 weeks of age, classified as stage 4B, which necessitated a vitrectomy. Subsequently, the retina of the left eye was successfully reattached and maintained for over 6 months. No systemic complications except for prematurity were noted before and after the treatment.

Discussion

We have presented here a case of severe ROP treated with intravitreal bevacizumab. Although the effects of bevacizumab to halt the neovascularization of ROP were remark-

able, the consequent fibrosis of the FVM increased the magnitude of tissue traction, and deteriorated the TRD. Similar events are observed in severe proliferative diabetic retinopathy, a representative ischemic proliferative disorder of the eye which is treated by the intravitreal injection of bevacizumab [5, 6]. The development or progression of TRD is believed to be due to a rapid neovascular involution with accelerated fibrosis and posterior hyaloid contraction, as a response to decreased levels of VEGF. An acute contraction of the FVM in the natural course of aggressive ROP is often observed clinically. However, the present case showed an extremely fast contraction accompanied by fibrosis of the FVM within 24 hours post-injection without any progression of the disease in the other eye until 5 weeks later, which was considered an unusual course. Since many molecules such as VEGF, connective tissue growth factor and transforming growth factor build a complex interaction to regulate angiogenesis and tissue fibrosis [7], our intervention might have unbalanced this interaction, and thus induced unexpected tissue contraction. Very recently, a significant increase in the intravitreal levels of VEGF was demonstrated in vascularly active stage 4 ROP [8]. Therefore, the intravitreal injection of bevacizumab should be recommended before the onset of stage 4.

In conclusion, the intravitreal injection of bevacizumab is a powerful modality to maintain aggressive ROP. However, IVB might exacerbate the progression of TRD in some specific cases.

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