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Diagnosis/Therapy in Ophthalmology

Fluorescein angiography of aggressive posterior retinopathy of prematurity treated with intravitreal anti-VEGF in large preterm babies

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Case 1

A premature baby boy born at 30 weeks gestation weighing 1600 g at birth was transferred to our institution for treatment of retinopathy of prematurity (ROP) at 32 weeks premenstrual age (PMA). The patient had respiratory distress syndrome immediately after birth requiring mechanical ventilation and received one dose of surfactant in the secondary hospital. He did not have patent ductus arteriosus (PDA), sepsis, intraventricular haemorrhage (IVH) and a history of blood transfusion. Initial examination disclosed bilateral aggressive posterior ROP (AP-ROP) in zone 1. At 32 weeks PMA, intravitreal ranibizumab (0.3 mg) was injected bilaterally. Fundus photographs and fluorescein angiography (FA) were taken using RetCam (Clarity Medical Systems, Pleasanton, CA) at pre- and post-treatment every month for 5 months after treatment (Fig. 1). Two months after treatment (40 weeks PMA), FA showed reactivation of conventional ROP and we again administered intravitreal ranibizumab (0.3 mg) by bilateral injection. At 2 months after the second injection (48 weeks PMA), leakages from the peripheral ridge were not observed and vessel tortuosity had significantly decreased, but the far peripheral retina had not fully vascularized (Fig. 1E).

Case 2

A premature baby boy born at 33 weeks gestation weighing 1950 g at birth was transferred to our institution for treatment of ROP. The patient had apnoea and received supplementary oxygen supply for 9 days after birth in the secondary hospital. He did not have PDA, sepsis, IVH and a history of blood transfusion. The infant was diagnosed as bilateral AP-ROP in zone 1 at 35 weeks PMA. At 35 weeks PMA, a bilateral intravitreal bevacizumab (0.625 mg) injection was performed. Serial pre- and post- treatment fundus photographs and FA were taken (Fig. 2). At 5 months after treatment (55 weeks PMA), the point leakages had decreased and the far peripheral retina had not fully vascularized (Fig. 2F).

Case 3

A premature baby boy born at 30 weeks gestation weighing 1690 g at birth was transferred to our institution for treatment of ROP. The patient received supplementary oxygen supply for 20 days after birth in the secondary hospital. He did not have PDA, sepsis, IVH or a history of blood transfusion. An initial examination at 31 weeks PMA disclosed immature vessels in zone 1 with preplus disease; he progressed to AP-ROP with Plus disease by 35 weeks PMA. At 35 weeks PMA, intravitreal bevacizumab (0.625 mg) was injected bilaterally. Before the injection, a bilateral fundus photograph showed severe vessel tortuosity, loop-shaped vessels and flat neovascularization with haemorrhages. Retinal vessels growth was limited to posterior zone 1 (Fig. 3A). FA was not taken before the injection. At 2 months after the injection (39 weeks PMA), vessel tortuosity and flat neovascularization had disappeared and normal retinal appearance was observed (Fig. 3B). At 3 months after injection (43 weeks PMA), branches of retinal vessels that had a brush border-like appearance and lines at the V-Av junction had developed with vessel tortuosity. We regarded the findings as a reactivation of ROP had occurred and performed laser photocoagulation at the peripheral avascular retina (Fig. 3C). At 4 months after laser treatment (59 weeks PMA), FA showed a normal retinal appearance in the vascularized area without leakages. However, a few leakages were observed in the peripheral retina burned with the laser. The leakages originated from the ends of the vessels that had grown over the V-Av junction (Fig. 3D). Additional laser treatment was performed. Two months later (67 weeks PMA), the leakages had almost disappeared (Fig. 3E).

AP-ROP is usually seen in extremely premature babies having gestational

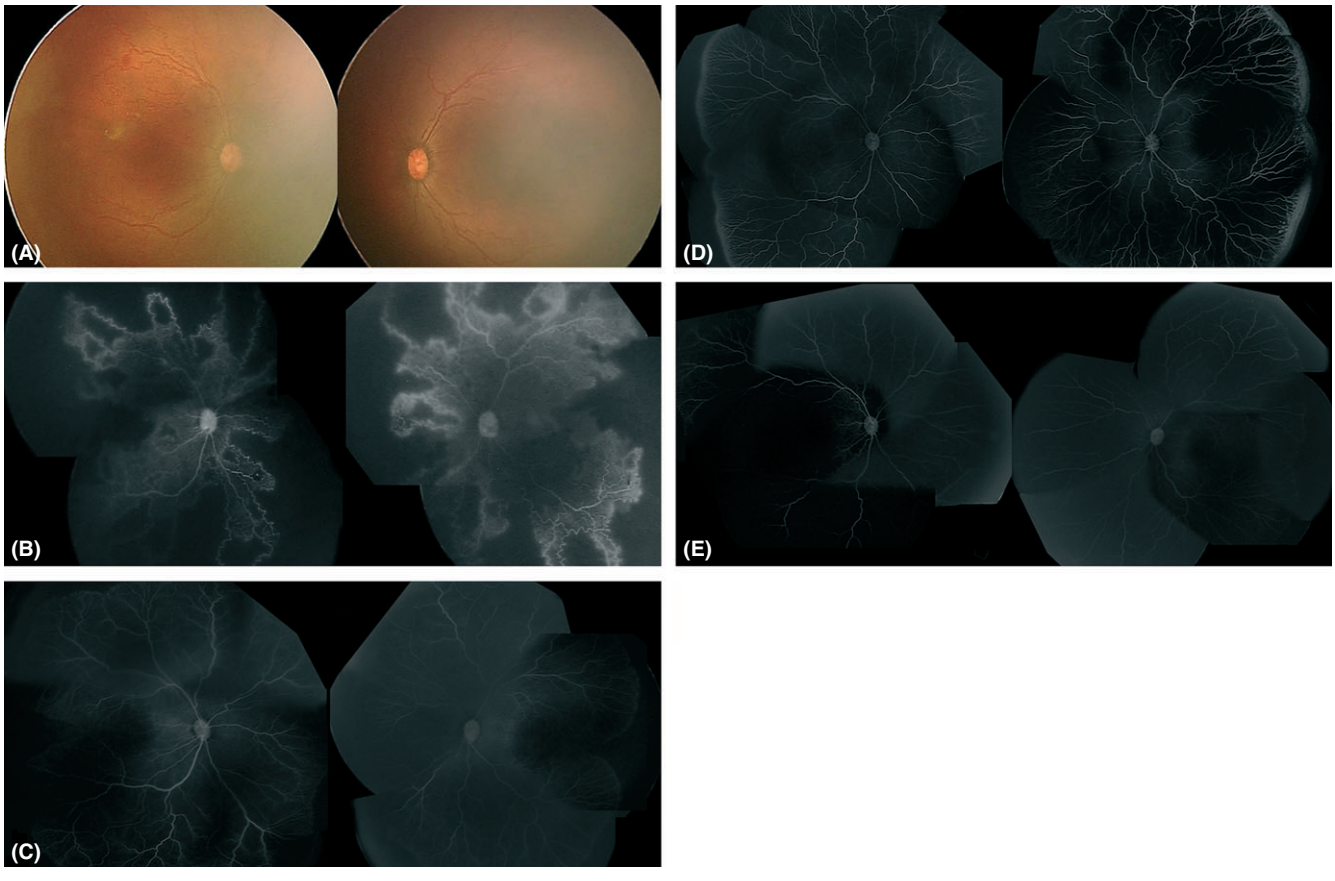

Fig. 1. Bilateral fundus photographs and montage fluorescein angiography (FA) of aggressive posterior retinopathy of prematurity of case 1. (A) Fundus photograph before treatment shows severe vessel tortuosity, a few haemorrhages with plus disease and immature development of the retinal vessels that ceased in zone 1. (B) FA before treatment shows a significant delay of choroidal filling, loop-shaped large arteriovenous shunts, capillary non-perfusion inside loop and leakages from diffuse flat neovascularization and arteriovenous shunt vessels. (C) One month after treatment, FA shows stabilization and growth of retinal vessels without leakages. (D) Two months after treatment, FA shows leakages at bilateral temporal vascular and avascular retina junction with plus disease. (E) Three months after second ranibizumab treatment, FA shows stabilized retinal vessels, no leakages and a far peripheral retinal avascular area.

age (GA) of <28 weeks and birth weight (BW) <1000g. In a study performed in India, Shah et al. (2012) observed AP-ROP in infants with a heavier BW and more advanced GA at birth. They stated that this could be related to inappropriate unblended oxygen treatment during the perinatal period. They showed that the retinal vessels initially observed in zone 2 and 3 (as would be expected of babies born at 33-35 weeks GA), later regressed to zone 1, making the baby susceptible to AP-ROP. In our study, all three infants had GA of over 30 weeks and BW exceeding 1500 g, and had no risk factors of ROP including PDA, sepsis and a history of blood transfusion. All infants were transferred from the same secondary hospital between August 2011 and May 2012. With the exception of that period, we have not seen large preterm babies with AP-ROP that were transferred or born at our hospital. Although we were not able to obtain the records of their oxygen concentration for treatment from that hospital, we assumed that inappropriate oxygen treatment might cause AP-ROP in our cases such as the study of Shah et al.

Yokoi et al. (2009) showed FA characteristic findings of AP-ROP in extremely premature infants. Their mean GA and BW were 24 weeks and 600 g, respectively. Even when ROP stabilized after laser or surgical treatments, vascular abnormalities remained, including hypoplastic macular vessels, loss of the arcade pattern, four small major vessels, and insufficiency of the capillary-free zone in the fovea. They concluded that long-term good visual acuity was doubtful due to poor macular function. Lepore et al. (2011) showed many characteristic FA findings of ROP undergoing laser treatment. Among them, two cases were AP-ROP that showed an absence of the foveal avascular zone and zone 1 with a massive extent of hypofluorescent areas. They were also extremely preterm infants. In our cases, the aforementioned abnormal vascular findings were not shown after anti-VEGF treatment. These findings differed in large preterm babies from those in extremely preterm infants. Also, in the study by Shah et al. (2012), 92% of large preterm babies with AP-ROP had a visual acuity of $\geq 20/60$ at a mean follow-up of 3 years. This shows a preserved macular function in large preterm babies with AP-ROP.

This study has an advantage of showing vascular development after intravitreal anti-VEGF injection by undertaking serial FA. In case 1 and 2, we conducted FA up to 5 months after treatment considering that the mean time to recurrence was 16 weeks

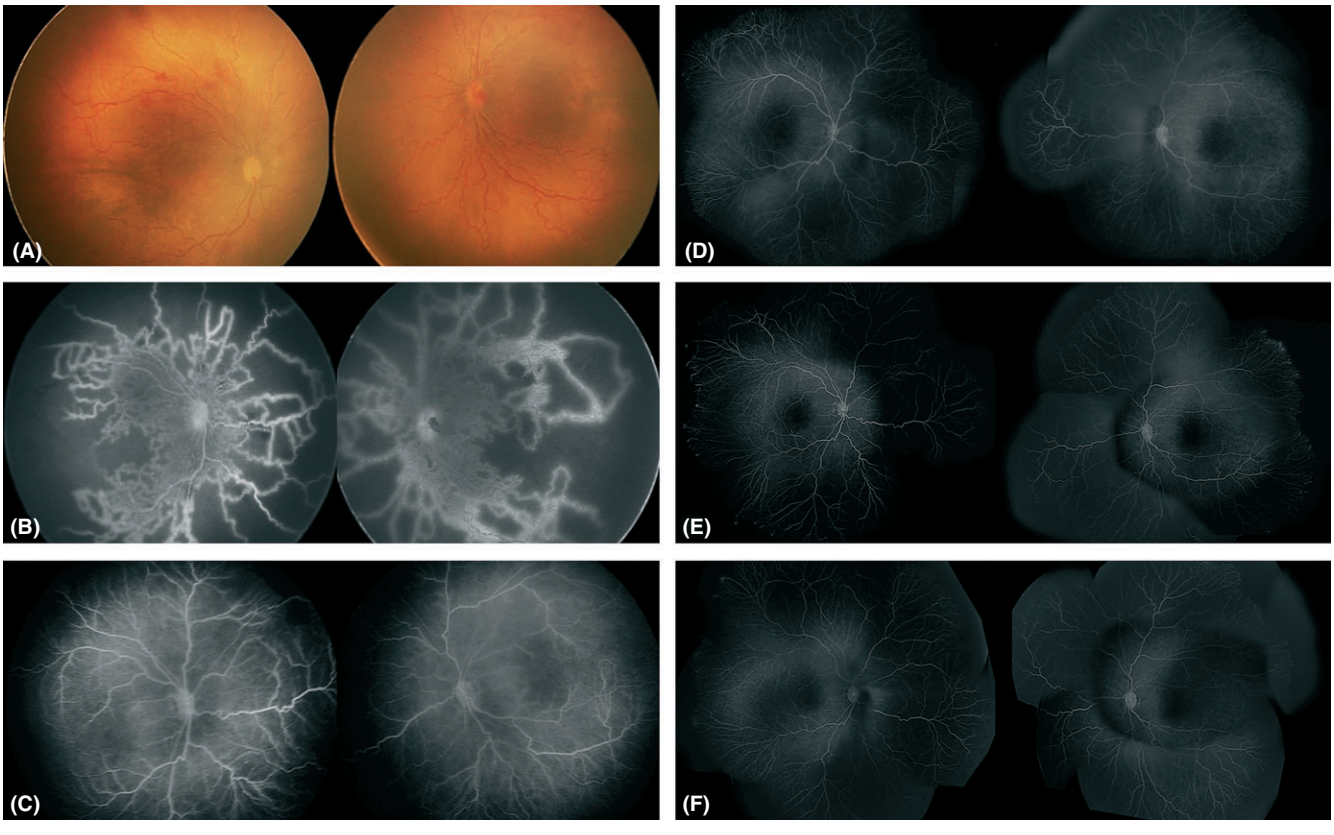

Fig. 2. Bilateral fundus photographs and montage fluorescein angiography (FA) of aggressive posterior retinopathy of prematurity of case 2. (A) Fundus photograph before treatment shows severe vessel tortuosity, loop-shaped large vessels, a few haemorrhages with plus disease and immature development of the retinal vessels that stopped in zone 1. (B) FA before treatment shows a significant delay of choroidal filling, loop-shaped large arteriovenous shunts, capillary non-perfusion inside loop and leakages from diffuse flat neovascularization and arteriovenous shunt vessels. (C) One month after treatment, FA shows relatively normal choroidal filling, and stabilization and growth of retinal vessels without significant leakages. (D) Two months after treatment, montage FA shows that retinal vessels grew and reached at zone 2. (E) Four months after treatment, montage FA shows terminal point leakages at the bilateral temporal vascular and avascular junction. (F) Five months after treatment, montage FA shows decreased terminal point leakages and a far peripheral retinal avascular area.

after intravitreal bevacizumab injection in the BEAT-ROP study (Mintz-Hittner et al. 2011).

Fluorescein angiography of case 1 showed stabilization and growth of retinal vessels at 1 month after intravitreal ranibizumab injection. However, at 2 months after treatment, a reactivation of conventional stage 3 ROP at zone 2 with Plus disease occurred bilaterally. At 3 months after the second intravitreal ranibizumab injection, abnormal leakages or abnormalities of vessels were not observed, with the exception that the far peripheral retina did not fully vascularize. The recurrence pattern of our case showed a conventional zone 2 ROP, and the time to recurrence was relatively short (4 weeks) compared with that in bevacizumab treatment (mean, 16.6 weeks) (Mintz-Hittner et al. 2011).

Case 2 showed a good result without a recurrence. However, the far peripheral retina did not fully vascularize as it had in case 1, and vascular terminal point leakages on the temporal V-Av junction showed at 4 months and decreased at 5 months after bevacizumab treatment. In case 3, a few leakages were observed in the peripheral retina burned with the laser. The leakages originated from the ends of the vessels that had grown over the V-Av junction at 7 months after injection. In addition, the leakages had almost disappeared after the added laser treatment.

Mintz-Hittner et al. (2011) stated that after intravitreal bevacizumab, the retinal vessels advance to the point at which the vascular precursors have ceased migration, with differentiation of the underlying retina. However, the vascular precursors do not advance; thus, the far peripheral retina never fully vascularizes and does not differentiate. If the peripheral avascular area was small and retinal vessels were stable like case 1 and 2, prophylactic laser treatment would not be considered. However, if a large avascular area remained, laser treatment would help prevent the recurrence of ROP. Pretreatment FA can be helpful in evaluation of capillary non-perfusion area, but a follow-up with only retinal inspection without FA is considered to be sufficient. Follow-up is needed in infants treated with intravitreal anti-VEGF injection, until there is completion of vascularization with no active disease (Mintz-Hittner et al. 2011).

This is the first study in which serial FA was performed on large preterm babies with AP-ROP. FA showed a significant delay of choroidal filling, loop-shaped large arteriovenous shunts and capillary non-perfusions. Leakages from diffuse flat neovascularizations and arteriovenous shunt vessels were shown. After intravitreal anti-VEGF injection, retinal vessels stabilized and

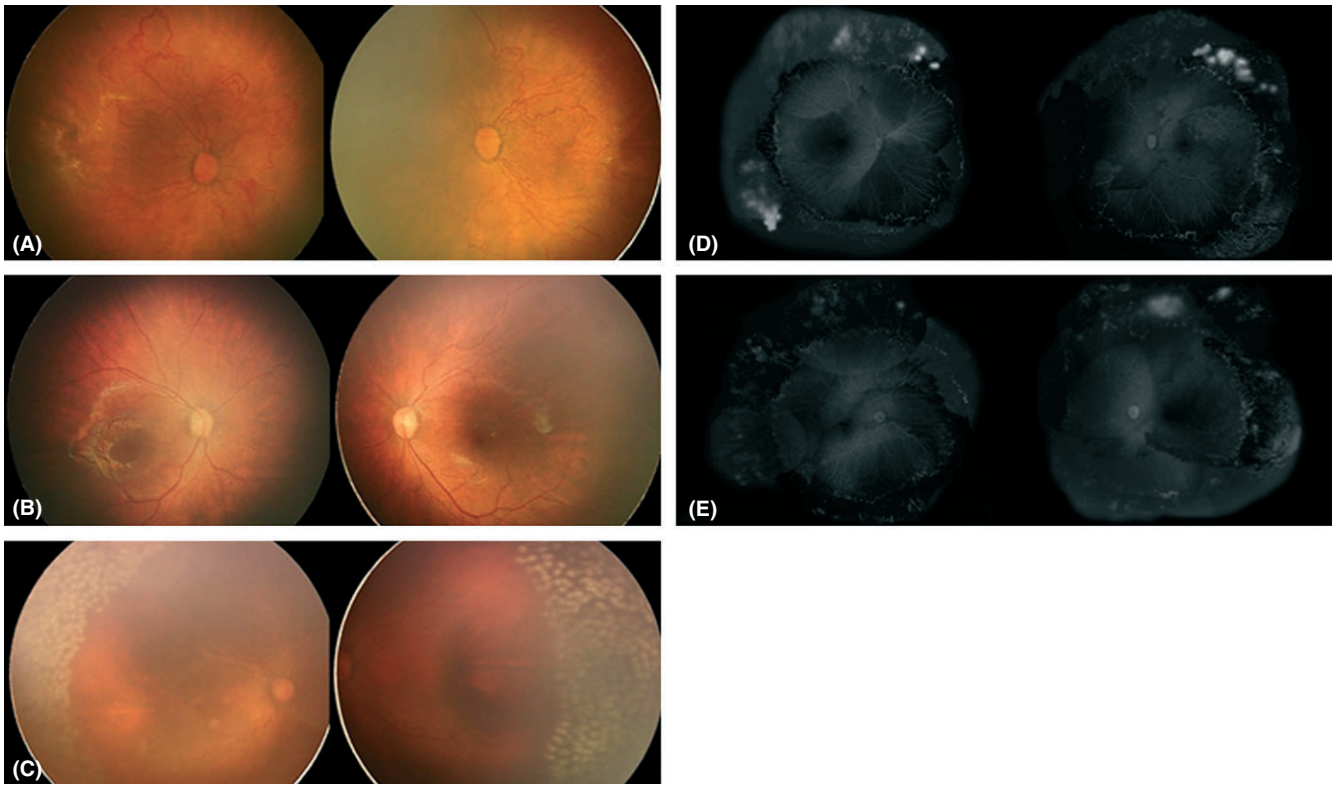

Fig. 3. Bilateral fundus photographs and montage fluorescein angiography (FA) of aggressive posterior retinopathy of prematurity of case 3. (A) Fundus photograph before treatment shows severe vessel tortuosity, loop-shaped large vessels and a few haemorrhages with flat neovascularization and immature development of the retinal vessels that had ceased in posterior zone 1. (B) Two months after treatment, stabilization and growth of retinal vessels were shown in bilateral fundus photographs. (C) Three month after treatment, fundus photographs show branches of retinal vessels with a brush border-like appearance and lines at the vascular and avascular (V-Av) junction with vessel tortuosity, and laser burns at peripheral avascular retina are shown. (D) Four months after laser treatment, montage FA shows normal retinal vascular appearance in vascularized area without leakages. However, a few leakages are observed in the peripheral retina burned with a laser. The leakages are from the ends of vessels that grew over the V-Av junction. The retinal vessels developed and reached at zone 2. (E) Two months after the second laser treatment, montage FA shows the leakages have nearly disappeared.

grew to the periphery of the retina. The far peripheral retina did not fully vascularize and a few terminal point leakages could be shown. Different from extremely preterm babies with AP-ROP, significant delay choroidal filling was shown before treatment and vascular abnormalities including hypoplastic macular vessels, loss of the arcade pattern, four small major vessels and insufficiency of the capillary-free zone in the fovea were not shown in large preterm babies with AP-ROP after anti-VEGF treatment.

This study will help to understand the mechanism and anti-VEGF treatment outcomes in large preterm babies with AP-ROP.

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