Intravitreal Bevacizumab for Incontinentia Pigmenti

Parag K. Shah, DNB; Sandeep Bachu, DNB; Venkatapathy Narendran, DNB; Narendran Kalpana, DNB; Jeevamala David, DNB; Chakravarthi R. Srinivas, MD, FRCP

ABSTRACT
Two eyes of two siblings affected with incontinentia pigmenti having severe proliferative retinopathy are reported. Both cases showed complete resolution of new vessels after a single injection of intravitreal bevacizumab. At 7 months of follow-up, the first case revealed vascularization to the mid-periphery including a vascularized fovea (which was avascular before injection) but recurrence of some peripheral neovascularization, which was treated by conventional laser. The second case had no recurrence. No ocular or systemic adverse effects were observed. Intravitreal bevacizumab as an adjunct therapy in incontinentia pigmenti with macular ischemia could be beneficial. [J Pediatr Ophthalmol Strabismus 2013;50:e52-e54.]

INTRODUCTION
Incontinentia pigmenti is a rare, X-linked dominant disorder in which affected female infants develop characteristic abnormalities of the skin, central nervous system, hair, teeth, and eyes. Ocular abnormalities consist of proliferative vitreoretinopathy and retinal detachment. Retinal vascular abnormalities, ranging from peripheral retinal avascularity to neovascularization to traction retinal detachment, are the primary cause of severe visual dysfunction in patients.1 Therapeutic intervention with laser photocoagulation or cryotherapy for the proliferative vitreoretinopathy of incontinentia pigmenti has met with variable success.2 We report two cases of severe proliferative retinopathy with ischemic macula in which intravitreal bevacizumab was associated with a dramatic response.

CASE REPORTS
Case 1
A 15-day-old female infant was referred from the dermatology department in February 2010 for ophthalmic evaluation. Antenatal history was uneventful and the infant was born by full-term normal vaginal delivery with a birth weight of 2,900 g with normal APGAR score. Family history revealed that the mother had three previous abortions prior to this pregnancy. The first child was a stillborn male child at 28 weeks of gestation. The other two abortions were at 2 and 3 months, respectively, with the gender of the children not known.

On general examination, multiple linear vesicles and crusted lesions with pigmentation were seen over the skin of all four limbs, maximum in the left leg (Figure 1), and also a few crusted lesions on the scalp and axilla. Skin biopsy was consistent with incontinentia pigmenti. The mother had a few cutaneous lesions over the right foot, but no dental or ocular abnormalities were seen in her.
On anterior segment examination, the child’s right eye was normal and the left eye showed small rigid pupil with neovascularization of iris. On fundus evaluation, the right eye showed a few superficial retinal hemorrhages nasally with a small area of avascular retina in the nasal periphery. The left eye revealed vitreous haze with dilated posterior pole vessels, retinal neovascularization, and vitreous hemorrhage along with extensive 360° avascular area involving even the fovea (Figure 2A).

Due to poor dilation, vitreous haze, and lack of foveal vascularization, primary laser treatment was not attempted. After receiving approval from the local ethical committee and informed consent from the parents, 0.03 mL of intravitreal bevacizumab (Avastin; Genentech, Inc., San Francisco, CA) was injected in the left eye. On the first postoperative day, the left eye revealed complete disappearance of iris new vessels with marked reduction in caliber of posterior pole vessels. The child was observed weekly for 2 weeks, then every 2 weeks for 1 month and monthly thereafter.

At 7 months postoperatively, the left eye revealed increased posterior pole vessel caliber and new vessels 3 disc diameters temporal to the fovea, which was confirmed on fluorescein angiography (Figure 2B). Laser photocoagulation to the entire peripheral avascular retina was given with diode green laser treatment (Aurolase 532; Aurolab, Madurai, India). One month after laser photocoagulation, there was complete regression of new vessels. At the end of 30 months of follow-up, corneal reflex and cover test were normal in both eyes and she could fixate and follow the light with the left eye. The patient developed myopic astigmatism in that eye for which glasses were prescribed along with 2 hours per day occlusion of right eye. The right eye was normal.

Case 2

The mother delivered another female infant in May 2012. She also had cutaneous lesions on all of the limbs. Fundus examination of this child revealed mild tortuosity of posterior pole vessels with the vessels reaching to the ora serrata in the right eye, whereas the left eye revealed a large temporal avascular retina, with preretinal hemorrhage involving the macula (Figure 3A). The left eye was given intravitreal Avastin after informed consent was obtained. At 11 months of follow-up, the vessels were within 1 disc diameter from the ora serrata temporally in the left eye with vascularized fovea, which was confirmed on fluorescein angiogram (Figure 3B). The child could fix and follow the light with each eye separately. No neurological abnormalities were seen in either infant.

**DISCUSSION**

Proliferative retinopathy seen in incontinentia pigmenti shares some common features with retinopathy of prematurity, namely an extensive avascular
retina and development of extraretinal neovascularization that may lead to fibrovascular proliferation and ultimately tractional retinal detachment. It usually presents in the first year of life, and early diagnosis and management improves visual outcome. Peripheral retinal ablation by cryotherapy or laser photocoagulation are beneficial in preventing progression to proliferative vitreoretinopathy and retinal detachments. However, there have been cases in which photocoagulation and cryotherapy failed to arrest fibrovascular proliferation. Use of intravitreal bevacizumab has been reported in incontinentia pigmenti, but as an adjunctive therapy prior to retinal detachment surgery. In our cases, primary laser photocoagulation or cryotherapy were avoided due to rigid pupil and vitreous haze in case 1 and lack of foveal vascularization in both cases.

To allow time for development of normal vascularization around the fovea, we injected intravitreal bevacizumab as an initial treatment. An immediate and dramatic response was noted, which was maintained until 7 months postoperatively in case 1 and was supplemented with laser photocoagulation when new vessels returned. In case 2, normal vascularization was seen to grow almost to the ora serrata. This could be because this case was less severe compared to the elder sibling.

Ischemic maculopathy has been described previously and can lead to irreversible macular infarction. The cutaneous cells in incontinentia pigmenti expressing muted X chromosome exhibited a reduced rate of free nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) and thus are more sensitive to the apoptotic signals. Furthermore, NF-kB is one of the links of the transduction system of the messages received by the vascular endothelial growth factor receptor. Similar to the cutaneous cells and cerebral microvascularization, a perturbation of the transmission of this message might also alter retinal microvascularization. By suppressing these receptors by its anti-vascular endothelial growth factor action, bevacizumab may delay this apoptosis of retinal vessels and allow the vessels to grow normally. To the best of our knowledge, this is the first report in which intravitreal bevacizumab, given as an adjunct treatment in incontinentia pigmenti with macular ischemia, yielded good results.

REFERENCES