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Asymmetric retinopathy of prematurity in presumed fungal endophthalmitis

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ABSTRACT

Purpose: To report a case of asymmetric retinopathy of prematurity (ROP) in a neonate with endophthalmitis.

Observations: A 25-week old female was born by caesarean section due to preeclampsia. The patient required supplemental oxygen after birth. The neonatal period was complicated by sepsis secondary to necrotizing enterocolitis with intestinal perforation. The patient subsequently developed endophthalmitis in the right eye. A fungal ball was seen overlying the termination of a persistent hyaloid artery. The patient also had ROP, identified at 31 weeks postconceptional age, which progressed asymmetrically and demonstrated greater severity in the eye affected by endophthalmitis. The endophthalmitis resolved with intravitreal antifungal treatment and systemic therapy. The right eye was also treated with intravitreal bevacizumab, demonstrating regression of ROP severity on follow up.

Conclusions and Importance: The present case describes the first reported case of asymmetric ROP associated with endophthalmitis. The more severe ROP occurred in the eye with endophthalmitis suggesting that, outside of systemic factors, the local ocular inflammatory environment is important in determining the progression of ROP. Additionally, the fungal ball present in the eye affected by endophthalmitis was seen at the termination of the hyaloid artery, suggesting the hyaloid artery as the route of entry of the fungus into the vitreous.

1. Introduction

Maturation of the retinal vasculature begins during the 16th week of gestation, starting from the optic nerve and extending peripherally in a centrifugal manner.[1] Retinopathy of prematurity (ROP) occurs when this process of vascularization is incomplete and areas of the retina are left nonperfused.

Retinopathy of prematurity is a biphasic disease. The developing retina becomes hyperoxic in preterm infants receiving supplemental oxygen. During this initial stage, the vaso-oblerative phase of ROP, retinal vessel growth is inhibited.[2] The state of hyperoxia causes suppression of vascular endothelial growth factor (VEGF) and other angiogenic factors. Subsequently, in the following vasoproliferative phase, from a postconceptual age (PCA) of about 31–36 weeks, the nonperfused areas of retina become ischemic, which triggers a signaling cascade that can result in neovascularization.[1–4]

Low birth weight, low gestational age, and the use of supplemental oxygen therapy after delivery are considered the greatest risk factors for the development of ROP.[5–8] Neonatal sepsis, in prior investigations, was also found to be associated with increased severity of ROP.[9,10] Several purported explanations for this association have been made. Sepsis may lead to increased oxygen demand and decreased systemic perfusion and oxygen delivery, worsening hypoxia and potentiating the vasoproliferative stage of ROP.[11] Furthermore, the upregulation of inflammatory cytokines may also contribute to vasoproliferation.[12,13]

The present report describes a case of unilateral endophthalmitis leading to asymmetric worsening of ROP in the affected eye. The theorized mechanism is a local upregulation of inflammatory cytokines causing an increase in neovascularization through oxygen sensing transcription factors.

2. Case report

A female neonate was born by caesarean section for preeclampsia at 25-weeks of gestation and 670g. Besides preeclampsia, the mother had had routine and unremarkable prenatal care.

The patient required mechanical ventilation after birth. Additionally, the patient developed necrotizing enterocolitis with intestinal perforation and subsequent sepsis. Blood cultures grew *Enterococcus faecalis*. Echocardiogram demonstrated mitral valve vegetations with septic embolization to the patient's right foot causing dry gangrene (Fig. 1). Liver ultrasound demonstrated lesions thought to

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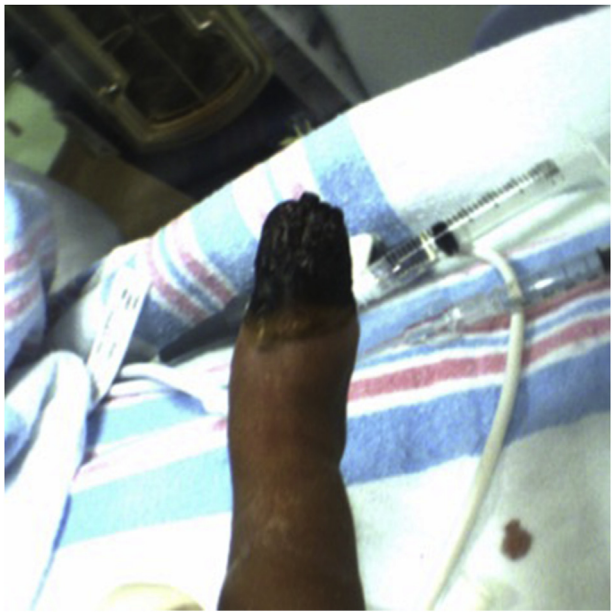

Fig. 1. Septic embolization causing dry gangrene of the right foot.

represent fungal hepatic abscesses. At the outside hospital, the patient was treated with 6 weeks of systemic antibiotics as well as antifungal prophylaxis with fluconazole without improvement.

At 31 weeks PCA, the patient was evaluated by the ophthalmology service at the outside hospital. Fundus examination raised concern for ROP in both eyes and endophthalmitis in the right eye. The patient was subsequently transferred to a tertiary referral center for evaluation by a pediatric retina specialist.

At the time of transfer to our institution, the patient was 32 weeks and 3 days PCA. On fundus examination, a white vitreous collection with features suggestive of a fungal ball was seen in the right eye adjacent to the termination of the hyaloid artery (Fig. 2). ROP was noted in both eyes. The right eye was diagnosed with stage I ROP extending to the border of zone I and zone II with 12 clock hours of involvement (Fig. 3A). Examination of the left eye disclosed stage I disease in zone II and 12 clock hours of involvement (Fig. 3B). Neither eye had plus disease.

Based on clinical examination, Candida endophthalmitis was suspected, and the patient was injected with intravitreal voriconazole in the right eye.[14,15] A concurrent vitreous tap was performed. The patient was started on systemic amphotericin. Vancomycin, cefepime, and metronidazole were restarted by the infectious disease service though repeat blood cultures, urine cultures, and cerebrospinal fluid cultures were negative, as there was concern for portal venous gas suggesting persistent intestinal perforation on abdominal ultrasound.

The vitreous culture did not demonstrate growth of any organisms. However, the suspected fungal ball improved with intravitreal voriconazole, and the injection was repeated in the right eye one week later. Repeat imaging of the abdomen with MRI did not demonstrate evidence of necrotizing enterocolitis so the vancomycin, cefepime, and metronidazole were discontinued.

Repeat fundus examination demonstrated resolution of the presumed fungal ball in the right eye 3 weeks after the initiation of treatment along with regression of the hyaloid artery. Additionally, the hepatic abscesses improved with systemic amphotericin treatment. However, at this time the ROP was asymmetric with more severe disease in the right eye. At 37 weeks PCA, the right eye had progressed to stage III disease in zone II (Fig. 4A), while the left eye remained at stage I (Fig. 4B). The patient was injected with intravitreal bevacizumab in the right eye for worsening ROP. At 42 weeks PCA, the ROP had regressed to stage 1 in the right (Fig. 5A) and left (Fig. 5B) eyes.

On subsequent evaluation in the outpatient clinic at 54 weeks PCA, the ROP remained symmetric and regressed to stage I disease in Zone 3. At last follow up at 2 years and 8 months chronological age, the vision was 6.5cy/cm in the right eye and 9.8cy/cm in the left. The vision in the right eye was decreased relative to the left likely because of mixed mechanism amblyopia. The endophthalmitis had cause deprivation secondary to the opacification of the visual axis in the setting of dense vitritis. Additionally, the patient's refraction revealed anisometropia with myopia ($-2.50 + 1.00 \times 091$) in the right eye and hyperopia ($+2.25 + 0.25 \times 077$) in the left. The patient was undergoing treatment with patching of the left eye.

3. Discussion

The present case of endophthalmitis in a premature neonate with several associated systemic complications is unique in that the presumed fungal endophthalmitis is likely to have seeded the eye through the hyaloid artery. Additionally, the endophthalmitis may have also caused asymmetric progression of ROP.

On initial examination, a fungal ball was seen at the end of the hyaloid artery. The hyaloid artery is a branch of the ophthalmic artery, which itself arises from the internal carotid artery. The hyaloid artery, extending from the optic nerve to the lens, normally regresses by 28–30 weeks PCA. However, up to 95% of premature neonates will demonstrate persistent hyaloid arteries, as in this case.[16] We postulate that the endophthalmitis seeded the eye through this persistent hyaloid artery. With intravitreal voriconazole, the endophthalmitis resolved and the hyaloid artery subsequently regressed.

Retinopathy of prematurity most commonly presents in a symmetric fashion. However, in a review of the CRYO-ROP data and subsequent investigations, approximately one-fifth of patients were found to present with asymmetric findings.[17] To date, the underlying etiology for asymmetry in ROP between fellow eyes of the same patient has not been elucidated. While post-gestational age, low birth weight, and the use of supplemental oxygen are clearly established risk factors for ROP, these are systemic risk factors presumably affecting both eyes

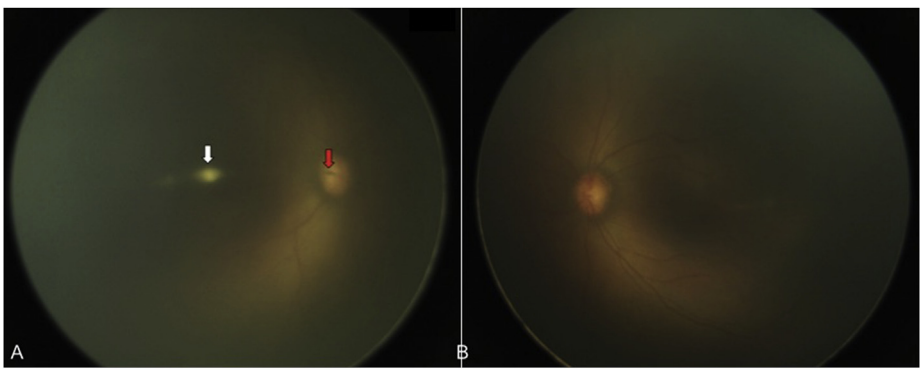

Fig. 2. Fundus photographs of the right and left eyes at approximately 33 weeks post-gestational age.
A.) The posterior pole demonstrates vitreous haze and a white vitreous lesion overlying the macula (white arrow) suggestive of a fungal ball adjacent to the termination of a persistent hyaloid artery (red arrow). B.) Fundus photograph of the posterior pole in the left eye does not demonstrate any lesions. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

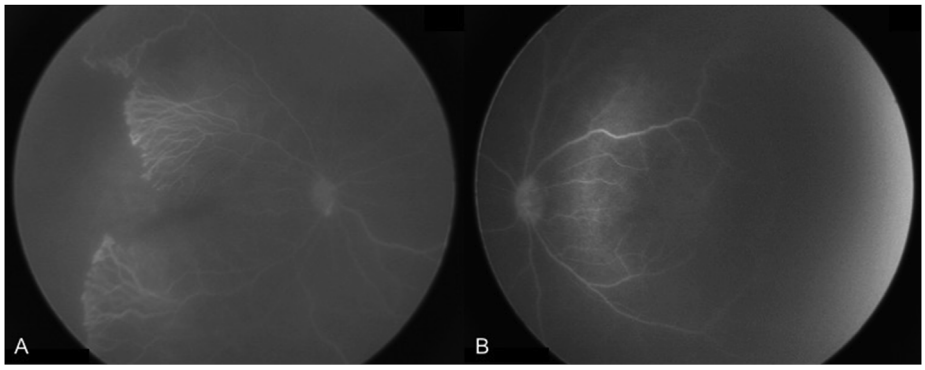

Fig. 3. Fluorescein angiography (FA) performed at approximately 33 weeks post-gestational age.
3A: FA of the right eye demonstrates retinal nonperfusion temporally at the border of Zone I and II.
3B: FA of the left eye demonstrates retinal nonperfusion (Stage I) in Zone II without evidence of neovascularization.

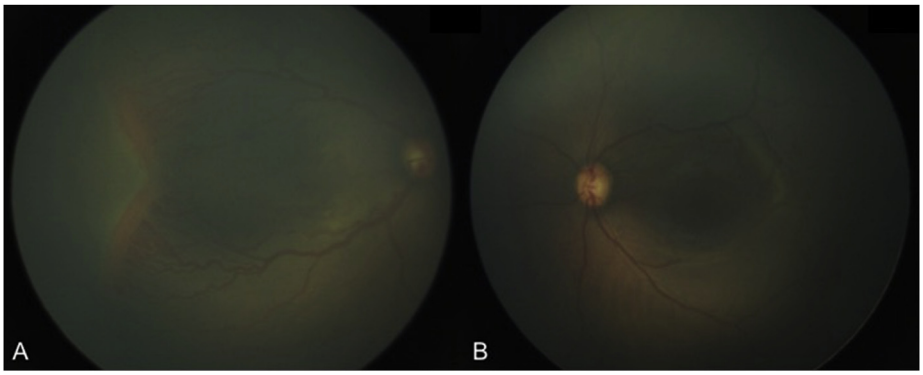

Fig. 4. Fundus photography performed at 37 weeks post-gestational age demonstrating asymmetric retinopathy of prematurity.
4A: The right eye demonstrates a temporal ridge with neovascularization consistent with Stage III disease. The previously noted vitreous lesion overlying the macula completely resolved and the persistent hyaloid artery regressed.
4B: The left eye demonstrates Stage I disease in Zone II.

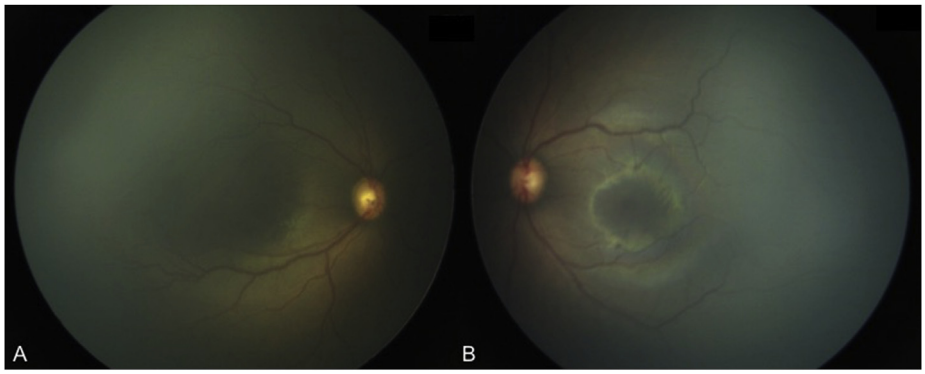

Fig. 5. Fundus photography performed at 42 weeks post-gestational age.
5A: The right eye demonstrates regression of the previously seen temporal ridge and associated neovascularization after treatment with a single intravitreal injection of bevacizumab.
5B: The left eye remained at Stage I disease in Zone II.

equally.[5–8]

Asymmetric presentation of ROP suggests that local environmental factors within each eye also influence the severity of ROP. In the present case, the patient presented with presumed fungal endophthalmitis in the right eye, which also demonstrated more severe ROP than the fellow eye. To our knowledge, this is the first reported case of endophthalmitis associated with asymmetric ROP.

Systemically, sepsis and elevated inflammatory cytokines have both been associated with increased severity of ROP.[12] Candida, in particular, has been shown to interact with vascular endothelial cells, causing release of inflammatory cytokines that injure developing retinal blood vessels.[18] We hypothesize that these same mechanisms occurring at a local level in the right eye caused progression in the ROP compared to the left eye.

Another possible trigger for the asymmetric progression of the ROP in the right eye may have been treatment with intravitreal voriconazole. Voriconazole, a triazole, works by inhibiting the synthesis of ergosterol, which is used in the synthesis of the fungal cell wall.[14] However, in a study on chick chorioallantoic membranes, voriconazole did not demonstrate *in vivo* angiogenic effects.[19] Further, in vitro and animal studies have demonstrated a favorable safety profile for voriconazole in terms of retinal toxicity, cell proliferation, and cell viability.[20–23] Nevertheless, effects of voriconazole on progression of the ROP cannot be completely ruled out.

Treatment with intravitreal anti-VEGF led to regression of the ROP. The authors generally advocate if treating with anti-VEGF for ROP to treat both eyes. However, in this case there was a possible trigger for unilateral worsening of ROP and the asymmetric presentation, thus

treatment was only given to the eye with threshold disease. The eye not affected with endophthalmitis did not progress and did not require treatment.

While ROP most commonly presents symmetrically, understanding the etiology behind asymmetric ROP may lead to a better understanding of the factors that potentiate the progression of disease. The present case, with unilateral endophthalmitis leading to progression of ROP in the affected eye, highlights the potential importance of local oxygen tension and inflammatory factors in the development of asymmetric ROP.

Patient consent

Written consent to publish this case has not been obtained. This report does not contain any personal identifying information.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

Financial interest

None.

Disclosures

None.

Declaration of competing interest

Dr Audina M. Berrocal reports the following disclosures: Administrative board member for Allergan PLC and Bayer; Consultant for Alcon, Dorc (Dutch Ophthalmic Research Center International BV), Visunex, and Phoenix.

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