# *Candida* (Amphotericin-Sensitive) Lens Abscess Associated With Decreasing Arterial Blood Flow in a Very Low Birth Weight Preterm Infant

Laura Drohan, MD*; Christopher E. Colby, MD*; Mary E. Brindle, MD‡; Steven Sanislo, MD§; and Ronald L. Ariagno, MD*

**ABSTRACT. In this report, we review the case of a candidal lens abscess in a premature infant girl who was 28 weeks' gestational age at birth. The culture obtained from the lens abscess grew *Candida albicans* sensitive to amphotericin B but resistant to flucytosine. This case is unique in that the infant developed a fungal lens cataract at 34 weeks' postconceptional age during the last week of a 30-day course of amphotericin B. The embryonic hyaloid artery system, which perfuses the developing lens, regresses between 29 and 32 weeks of gestation; thus, the mechanism for an infection of the lens may be inoculation of the lens by *Candida* before hyaloid artery system regression, followed by developmental loss of this blood supply, which makes the lens inaccessible to antimicrobial penetration. Candidal endophthalmitis with lens abscess is an uncommon morbidity that requires prompt recognition and surgical intervention for effective management. *Pediatrics* 2002;110(5). URL: http://www.pediatrics.org/cgi/content/full/110/5/e65; *low birth weight, preterm infant, candida endophthalmitis, lens abscess.***

ABBREVIATIONS. TVL, tunica vasculosa lentis; DOL, day of life; CSF, cerebrospinal fluid; ROP, retinopathy of prematurity; 5-FC, flucytosine.

Although *Candida* chorioretinitis is the most common presentation of an intraocular infection in the premature infant, candidal lens abscesses are uncommon.[1–4] An abscess in the lens, an apparently avascular structure, should be unlikely. However, during early embryologic development the lens has a blood supply from the hyaloid artery system supplied by the hyaloid artery, a tributary of the main ophthalmic artery. The hyaloid artery approaches the lens from the posterior side, supplying the posterior portion of a network of vessels enveloping the lens, the tunica vasculosa lentis (TVL). The TVL is also supplied along its equatorial margin by vascular branches fed by the long ciliary arteries.[5] The hyaloid artery regresses later in gestation. A transparent remnant, the canal of Cloquet is found when the lens becomes avascular. The TVL also involutes, generally later than the hyaloid artery. Once the hyaloid artery involutes, the TVL is then completely supplied by the long ciliary arteries.[5–7] We report a case of candidal endophthalmitis with lens abscess formation presenting initially as a cataract in a preterm infant at 30 weeks' postconceptual age. This case is unique because the infant developed the fungal cataract during systemic antifungal treatment. The cataract progressed to a *Candida albicans* lenticular abscess and endophthalmitis confirmed by lens culture. Aggressive surgical intervention and antifungal injection into the vitreous were required to resolve this infection and to salvage the left eye.

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## CASE REPORT

An infant girl was 28 weeks' gestational age at birth and weighed 1020 g. The pregnancy was complicated by premature labor at 24 weeks and premature rupture of membranes at 27 weeks' gestation. Initial sepsis evaluation was negative, and she received 5 days of ampicillin and gentamicin. She had 5 days of conventional mechanical ventilation for respiratory distress syndrome and was extubated to room air on day of life (DOL) 5. On DOL 16 (30 weeks' postconceptional age) she developed apnea and bradycardia requiring intubation and ventilatory support. Blood and urine cultures obtained at that time grew methicillin-resistant *Staphylococcus epidermidis*, for which she received 5 days of intravenous cefotaxime and 14 days of vancomycin treatment. Blood culture obtained 24 hours after initiation of antibiotics (DOL 17) was negative for *S epidermidis*; however, it was positive for *C albicans*. Amphotericin B was started at 0.5 mg/kg/d on DOL 18, and the percutaneously inserted central catheter that had been in situ for 14 days was removed. The catheter-tip Gram-stain showed budding yeast; however, the culture was negative. Lumbar puncture was performed 24 hours after initiation of antifungal therapy and revealed an elevated white blood cell count of 133/mm$^3$ (4% segmented neutrophils, 89% monocytes, 7% lymphocytes), red blood cell count of 2 and 5100/mm$^3$ (first and second tubes, respectively), glucose of 30 mg/dL, and protein of 126 mg/dL. Cerebrospinal fluid (CSF) and urine cultures were negative for bacteria and fungi. A blood culture drawn 72 hours after initiation of antifungal therapy was positive for *C albicans.* Blood cultures became sterile for fungus 5 days after antifungal treatment was started. A disseminated fungal workup, which included an echocardiogram, abdominal and head ultrasound, and ophthalmologic evaluation was negative. Intravenous amphotericin B was given for 30 days at 0.7 mg/kg/d. A lumbar puncture was repeated 2 weeks after initiation of amphotericin B and vancomycin, which demonstrated a decrease in the white blood cell count to 35/mm$^3$ (50% segmented neutrophils, 40% lymphocytes, 5% monocytes).

As part of the fungal workup, an ophthalmologic examination was done on DOL 28 and was normal. On DOL 42, a routine ophthalmologic examination, attributable to prematurity, revealed stage I retinopathy of prematurity (ROP) in zone III bilaterally, as well as a peripheral cataract in the left eye, which was suspicious

for *C albicans*. On DOL 48, after 30 days of systemic antifungal treatment, an ophthalmologic examination showed that the cataract was unchanged in appearance. The 30-day course of therapy was considered adequate, because blood cultures were sterile 5 days after initiation of the antifungal treatment, CSF cultures remained negative throughout, CSF pleocytosis resolved, and the cataract was not progressing. The patient received ophthalmologic examinations 7 and 14 days after discontinuation of antifungal therapy, which showed no change in the appearance of the cataract and resolving stage I ROP bilaterally. She was discharged from the hospital on DOL 72 (41 weeks' postconceptional age) with a scheduled ophthalmologic evaluation 1 week later. On DOL 78, the preexisting lens opacity had worsened and the iris vessels were engorged with evidence of uveitis. The child was referred to an ophthalmologist (S.S.) at our center and admitted, for the first time, to the neonatal intensive care unit at Stanford for presumed fungal endophthalmitis. She was started on amphotericin B and flucytosine (5-FC). On DOL 80, her endophthalmitis seemed worse, and ophthalmologic examination revealed complete opacification of the lens and increased shallowness of the anterior chamber. B-scan ultrasound showed a markedly echogenic lens and choroidal edema, without evidence of retinal involvement. These findings were consistent with the diagnosis of candidal endophthalmitis with lens abscess (Fig 1). Immediate operative intervention was recommended. The patient underwent left lensectomy and vitrectomy with intravitreal injection of amphotericin B and dexamethasone. *C albicans* (sensitive to amphotericin B and fluconazole, but resistant to 5-FC) grew from the lens abscess culture. Therefore, she was continued on intravenous amphotericin B and oral fluconazole was started. On DOL 92, an examination under general anesthesia showed marked improvement of the left eye, with decreased engorgement of iris vessels and no sign of persistent fungal endophthalmitis. Blood, urine, and CSF cultures were negative for fungi and bacteria during this hospitalization. The infant completed 14 days of amphotericin B and was subsequently discharged from the hospital to complete a total of 6 weeks of fluconazole. The latest follow-up at 7 months (5 months postlensectomy and vitrectomy) with one of us (S.S.) showed a quiet and clear anterior segment with a normal retina and no additional evidence of infection or inflammation.

## DISCUSSION

*C albicans* is a member of the genus *Candida*, which can be found as blastospore, chlamydospore, or forming hyphae or pseudomycelia. More than 150 *Candida* species have been described.[8] The pathogenesis of systemic candidal infection is dependent on the adherence of *Candida* blastospores to mucosal or dermal epithelial cells. It is spread hematogenously. The incidence of fungal infections is estimated to be 2% to 9% among very low birth weight infants (<1500 g).[9,10] The incidence of systemic candidiasis may be underreported, as only 50% to 80% of infected patients have positive blood cultures, and only 70% of those with meningeal involvement have positive CSF cultures.[11] The mortality of very low birth weight infants infected with *C albicans* ranges from 25% to 70% in published reports.[9,12–14] Risk factors for the development of systemic candidiasis include prematurity, especially when associated with low birth weight, sepsis, abdominal surgery, indwelling catheters, malnutrition, and treatment with multiple or broad-spectrum antibiotics.[15–17] In-

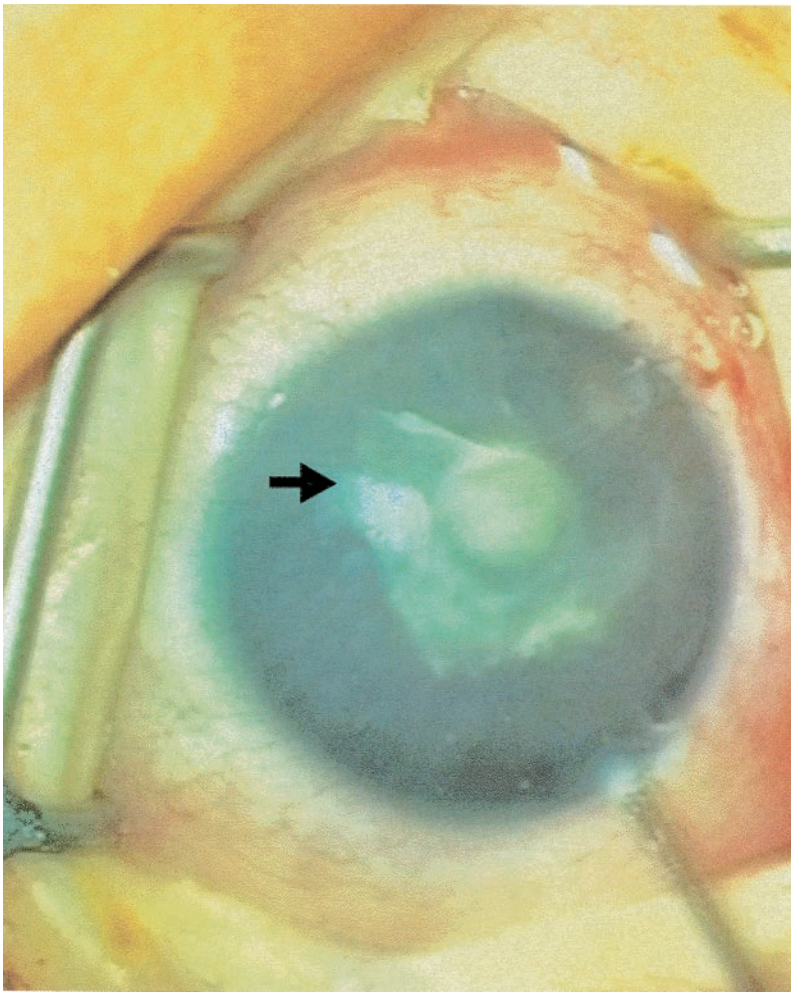

**Fig 1.** Preoperative photograph of the left eye showing opaque pupil with purulent material and fibrin in anterior chamber (arrow) from lens abscess after spontaneous rupture of anterior capsule.

fants who develop systemic candidiasis should be treated by removing all possible factors that predispose one to fungemia, initiating systemic antifungal therapy promptly, and thoroughly searching for additional foci of disease.[12] This investigation should include head and abdominal ultrasound; echocardiogram; ophthalmologic examination; blood, urine, and CSF cultures; and in some cases skeletal survey. Amphotericin B is the drug of choice for invasive candidiasis. The addition of 5-FC is recommended for central nervous system involvement by *C albicans*.[18,19] The addition of 5-FC remains controversial, as some series have demonstrated adequate fungal clearance from the CSF with amphotericin B alone. Moreover, 5% to 10% of *C albicans* isolates possess primary resistance to 5-FC, and *Candida* readily acquires resistance to the drug during treatment, with reports of up to 67% of yeasts becoming resistant in patients receiving 5-FC. Johnson et al[12] have advocated the use of initial combined therapy of amphotericin B and 5-FC in immunocompromised patients when clinical suspicion of invasive candidiasis exists. The *C albicans* isolated in this case was resistant to 5-FC; thus, failure to treat with 5-FC was not the cause of the lens abscess and endophthalmitis. Localized candidal infections generally develop secondary to hematogenous spread. The development of candidal abscess in an avascular structure is unusual. The late fetal regression of blood supply to the lens may provide some clues to the mechanism of infection in this case.

Studies using power Doppler show an intact hyaloid artery between 14 and 23 weeks of gestation. Between 24 and 28 weeks' gestation, 10% of fetuses had partial regression of the hyaloid artery; by 29 to 38 weeks' gestation, all had total regression.[6] These observations corroborated findings of an earlier report in which complete hyaloid artery regression was observed between 30 and 32 weeks' gestation.[7] The timing of this developmental regression of blood supply to the fetal lens suggests a potential window for initiation of infection in the lens and vitreous when the lens is vascularized, followed by resistance to antimicrobial and immune cell penetration once the lens is avascular. In the case of the patient, we speculate that there are at least 2 possible explanations about the hyaloid artery system involution for the infected lens. The first involves a hyaloid artery that was patent when the hematogenous infection occurred at 30 weeks' postconceptual age. Subsequently, the hyaloid artery circulation to the lens was decreasing or absent for the therapeutic penetration of amphotericin B into the lens. As a consequence, a fungal lens infection was established by 30 to 34 weeks' postconceptual age, after which the hyaloid artery regressed and the isolated lens infection progressed to a candidal lens abscess. The second scenario does not depend on the hyaloid artery, and instead focuses on the anterior portion of the TVL, supplied by the long ciliary arteries. [5] The TVL persists in many premature infants, long after shutdown of the hyaloid artery. It remains longer in those infants with higher stages of ROP. This is possibly because of higher intraocular levels of vascular endothelial growth factor, attributable to retinal ischemia. The TVL eventually involutes. As the vessels regress, they may go through a period of increased friability. Evidence for this is seen in infants undergoing laser or cryo treatment for ROP. The TVL rapidly involutes after treatment, most likely due to falling levels of vascular endothelial growth factor. Some of these infants develop transient, small anterior chamber hemorrhages (hyphemas) resulting from rupture of friable, involuting TVL vessels. Even without gross hemorrhage, friable involuting vessels may create a window for perilenticular seeding of fungal elements. Subsequent involution of the TVL would reduce penetration of antifungal agents to the lens area. The remaining nearby intraocular blood supply consists of the retinal vessels, which are more remote from the lens and have tight junctions, which would reduce drug penetration into the eye. The location of the infection, in an area surrounded by the TVL, suggests that these vessels may have been the portal of entry for the candida, arriving via the long ciliary arteries rather than by way of the hyaloid artery. By either scenario, the infected avascular lens represents an isolated infection inaccessible to systemic antifungal therapy. Candidal endophthalmitis with lens abscess is an uncommon morbidity. Early clinical diagnosis by the neonatologist, an ophthalmology consultation, and surgical intervention are essential for effective management and decreased eye morbidity.

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