

THE 4-1-1 ON INFECTIOUS RETINITIS



Challenges in the diagnosis and management of fungal endophthalmitis.

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Fungal endophthalmitis is a rare cause of infectious uveitis that can lead to severe intraocular inflammation and irreversible blindness. These infections can be classified as either exogenous or endogenous. In exogenous infections, fungal organisms from the ocular surface or an external source are introduced into the eye after trauma, surgery, or direct spread from fungal keratitis.¹ In endogenous infections, the fungi access the eye either through hematogenous spread associated with fungemia or, less commonly, from the central nervous system via the optic nerve.² In this article, we review diagnosis and management strategies for fungal endophthalmitis.

RISKS FACTORS AND PATHOGENESIS

Due to the rarity of fungal endophthalmitis, its exact prevalence is unknown. Although the prevalence of candidemia is thought to be on the rise due to the increased use of chemotherapy and immunosuppressive medications, the prevalence of endogenous endophthalmitis may be decreasing, as patients with positive blood cultures are commonly treated early with systemic antifungals.^{3,4} Among candidemia patients, the prevalence of endogenous fungal endophthalmitis ranges between 3% and 45%.^{5,6}

As noted above, endogenous fungal endophthalmitis usually results from the hematogenous spread of fungal organisms into the eye. Predisposing factors for infection include indwelling intravenous catheters, peripheral hyperalimentation, prolonged antibiotic or corticosteroid therapy,

immunosuppressive therapy, HIV infection, abdominal surgery, hemodialysis, malignancy, diabetes mellitus, alcoholism, pregnancy or postpartum state, and intravenous drug use.^{7,8}

Due to increased opioid abuse in the Eastern regions of the United States, the rate of endogenous fungal endophthalmitis associated with intravenous drug abuse has grown.⁸ The infection is thought to originate from fungal organisms entering the eye through a highly vascularized choroid. Chorioretinal seeding occurs prior to the involvement of the internal limiting membrane and vitreous. Tanaka et al developed a four-stage anatomic classification system in which a higher stage was correlated with a poorer final visual acuity, as well as with a delay between the presentation of initial symptoms and the diagnosis and initiation of therapy.^{9,10}

Risk factors for exogenous endophthalmitis include fungal keratitis,

penetrating trauma, and intraocular surgery. In these cases, the fungi may involve the anterior structures of the eye before affecting the vitreous and posterior segment.

The most common organism that causes endogenous infection is *Candida*, a yeast, followed by *Aspergillus*, a mold (Table). In endogenous infections after cataract surgery or trauma, the most common organism isolated is *Aspergillus*, followed by *Candida*.

CLINICAL PRESENTATION

The symptoms of fungal endophthalmitis are diverse and share similarities with other types of uveitis. In mild fungal endophthalmitis, the clinical features may be subtle and nonspecific, making for a challenging diagnosis. In a series of patients with endogenous fungal endophthalmitis, the initial rate of misdiagnosis was as high as 50%.¹¹ These patients may

AT A GLANCE

- Fungal endophthalmitis can be classified as either exogenous (infection following trauma, surgery, or direct spread from fungal keratitis) or endogenous (infection through hematogenous spread associated with fungemia or through the central nervous system via the optic nerve).
- Ocular signs of fungal endophthalmitis include anterior segment inflammation with hypopyon, keratic precipitates, and conjunctival injection.
- The role of pars plana vitrectomy in the management of fungal endophthalmitis is under debate due to a lack of large controlled studies.

TABLE. ORGANISMS THAT CAUSE INFECTION

	<i>Candida</i>	<i>Aspergillus</i>
Type of fungus	Yeast	Mold
More commonly found	Endogenous fungal endophthalmitis	Exogenous fungal endophthalmitis
First-line treatment	Amphotericin B or fluconazole	Voriconazole

present with decreased vision, photophobia, eye pain, and floaters.

Compared with bacterial endophthalmitis, the onset of symptoms in fungal endophthalmitis is typically more indolent and the degree of pain less severe. Ocular signs of fungal endophthalmitis include anterior segment inflammation with hypopyon, keratic precipitates, and conjunctival injection. In the posterior segment, fungal endophthalmitis may present with foci of chorioretinal yellow-white lesions, vitreous inflammation and haze, fungal

material in a “string of pearls” configuration, retinal hemorrhage, and vascular sheathing (Figure).

In later phases, a vitreous band may develop with the formation of an epiretinal membrane, causing retinal detachment. In exogenous cases spread from fungal keratitis, a white corneal infiltrate may be found with satellite lesions. Fungal endophthalmitis may present with a white plaque on the surface of an intraocular lens and mild vitritis, similar to delayed-onset post-cataract surgery endophthalmitis.¹²



Figure. Fungal chorioretinal lesion adjacent to the optic nerve with associated disc edema, intraretinal hemorrhages, and macular edema.

Aspergillus endophthalmitis can generally be associated with retinal or choroidal vascular occlusion and exudative retinal detachment, leading to a poorer prognosis than *Candida* endophthalmitis.^{4,13,14}

TESTING AND DIAGNOSIS

The diagnosis of fungal endophthalmitis relies on gram staining and aqueous or vitreous culture. This can be challenging, as fungal organisms are difficult to culture and have long incubation periods. In a patient with a clinically suspected endogenous fungal infection, a blood culture should be obtained. If the culture is negative, diagnostic vitrectomy may be performed. If there is a corneal infiltrate, corneal scrapings and cultures may aid in diagnosis. Before a definitive fungal endophthalmitis diagnosis is established, the use of broad-spectrum intravitreal antibiotics may be required in post-cataract surgery or post-trauma cases.

Fungal cultures from ocular fluid can be positive in 40% of vitreous samples, but the rate can increase to 70% with histopathology.^{15,16} Vitrectomy has the highest yield of all intraocular specimens. The highest yield fungal culture is from a vitrectomy sample (92%), compared with vitreous paracentesis (44%) and aqueous paracentesis (25%).¹⁷ As results of cultures may take several days and false negatives are possible, patients should be treated empirically with antifungal medications and may require concurrent broad-spectrum antibiotics.

The differential diagnosis of endophthalmitis is wide, including infectious causes of posterior uveitis (eg, syphilis, tuberculosis, and toxoplasmosis), acute retinal necrosis, intraocular lymphoma, tumor necrosis with inflammation, Vogt-Koyanagi-Harada disease, sympathetic ophthalmia, and sarcoidosis. It is important to have a low threshold of suspicion for fungal endophthalmitis, as steroidal treatments for uveitis

can worsen a fungal infection.

Depending on the clinical presentation, it may be appropriate to initiate a workup with a quantiferon-tuberculosis gold test, treponemal tests, toxoplasmosis titers, polymerase chain reaction analysis of aqueous fluid, and chest x-ray to rule out other infectious causes. Because an immunocompromised state is a risk factor, testing for concurrent HIV infection should be considered in the absence of other systemic illness.

CLINICAL MANAGEMENT AND VITRECTOMY

A systemic evaluation by an internist or infectious disease specialist may be necessary. There are two main classes of antifungal agents used to treat fungal endophthalmitis: polyenes and azoles. Other antifungal therapies such as echinocandins have poor ocular penetration and generally are not used to treat fungal endophthalmitis. Chorioretinitis may be treated with systemic antifungal drugs, but their vitreous penetration may vary. Therefore, intravitreal treatment may be required in cases of severe intravitreal inflammation.

Amphotericin B, a polyene, has the advantage of broad-spectrum coverage, but it has limited intraocular penetration and carries a risk of infusion-related toxicity and nephrotoxicity.¹⁸ As such, the preferred drug delivery option for this agent is intravitreal injection, but this has been associated with retinal toxicity and necrosis. Among the azoles, both fluconazole and voriconazole have good oral bioavailability and intraocular penetration.¹⁹ Systemic voriconazole is associated with hepatotoxicity and skin rash, so intravitreal administration may be preferred.¹⁹ The recommended first-line treatment for *Candida* endophthalmitis is amphotericin B or fluconazole, whereas voriconazole is recommended for *Aspergillus* endophthalmitis.¹⁹

It is important to note that

amphotericin B is considered safe in pregnancy (category B), whereas voriconazole is associated with a risk of fetal malformation in animal studies (category D).¹⁸

The role of pars plana vitrectomy (PPV) in the management of fungal endophthalmitis is under debate due to a lack of large controlled studies. PPV can decrease the infectious burden by removing fungi from the vitreous, while also clearing opacities, improving vision, and improving the diffusion of antifungal agents into the vitreous cavity.¹

In persistent cases of fungal endophthalmitis after cataract surgery, the intraocular lens may have to be removed at the time of PPV or during a second surgery. Serous, tractional, and rhegmatogenous retinal detachments can be associated with fungal endophthalmitis, and these can lead to poor visual outcomes. Although it is controversial, some retina specialists recommend early vitrectomy in which the posterior hyaloid is lifted to decrease the risk of future membrane formation and retinal detachment.^{1,20}

Depending on the location of fungal lesions and the virulence of the infectious organisms, the prognosis for fungal endophthalmitis is generally poor. A delay between diagnosis and treatment, a traumatic cause of the endophthalmitis, and the isolation of *Aspergillus* species are each associated with an unfavorable outcome. Eventual evisceration or enucleation occurs in 24% to 78% of cases.^{19,21}

POTENTIALLY DEVASTATING

Fungal endophthalmitis is a rare but potentially devastating infection. It is important to have a low threshold of suspicion for fungal infection to prevent delay in the onset of appropriate therapies. PPV may play an important role in the diagnosis and treatment of fungal endophthalmitis. Further developments to improve the

detection of fungal organisms from cultured fluid may aid in earlier diagnosis and improve prognosis. ■

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