Endogenous Fungal Endophthalmitis: Causative Organisms, Management Strategies, and Visual Acuity Outcomes

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• PURPOSE: **To report the causative organisms, management strategies, and visual outcomes in endogenous fungal endophthalmitis.**
• DESIGN: **Observational case series.**
• METHODS: **Microbiologic and medical records were reviewed retrospectively for all patients with culture-positive endogenous fungal endophthalmitis between January 1, 1990, and July 1, 2009.**
• RESULTS: **Study criteria were met in 65 eyes of 51 patients with mean follow-up of 18 months. Yeasts were the most common causative organism in 38 (75%) patients compared with molds in 13 (25%) patients. Retinal detachment occurred in 17 eyes (26%). Visual acuity of 20/200 or better was present in 28 (56%) eyes with yeasts and in 5 (33%) eyes with molds at the last follow-up.**
• CONCLUSIONS: **Yeasts were the most common cause of culture-proven unilateral or bilateral endogenous fungal endophthalmitis. Endogenous fungal endophthalmitis generally is associated with poor visual acuity outcomes, especially when caused by molds. Retinal detachment is a frequent occurrence during follow-up. (Am J Ophthalmol 2012;153:162–166. © 2012 by Elsevier Inc. All rights reserved.)**

ENDOGENOUS FUNGAL ENDOPHTHALMITIS IS A SERIOUS ocular condition with potentially devastating visual outcomes. Ocular seeding occurs through hematogenous spread and may involve both the anterior and posterior segments of the eye.[1] Most patients with endogenous fungal endophthalmitis have 1 or more predisposing systemic conditions, including risk factors such as recent hospitalization, diabetes mellitus, liver disease, renal failure, cancer, indwelling lines, systemic surgery, organ transplantation, HIV/AIDS, intravenous drug use, hyperalimentation, and immunosuppressive therapy.[2,3] Endogenous fungal endophthalmitis may occur rarely in healthy, immunocompetent patients without any risk factors.[4,5]

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Many fungi have been reported to cause endogenous fungal endophthalmitis. Most commonly, endogenous fungal endophthalmitis is associated with *Candida* or *Aspergillus* species.[2,3,6] Reported treatment regimens include various combinations of systemic and intravitreal antifungals as well as vitrectomy.

The current report represents a large consecutive series of patients treated at a single academic medical center for endogenous fungal endophthalmitis and includes the specific fungal isolates, treatment strategies, and visual acuity outcomes.

METHODS

MICROBIOLOGIC AND CLINICAL RECORDS WERE REVIEWED from all patients treated at Bascom Palmer Eye Institute (BPEI) between January 1, 1990, and July 1, 2009, for intraocular culture-proven endogenous fungal endophthalmitis (n = 51). After obtaining a list of the causative organisms, the corresponding medical records were reviewed for clinical presentation, treatment strategy, and outcomes. Study inclusion criteria were positive fungal culture results and clinical course consistent with endogenous fungal endophthalmitis.

Intraocular fluid specimens were plated directly on to chocolate agar, 5% sheep blood agar, and Sabouraud agar. Chocolate and blood agars were incubated at 35 C for up to 2 weeks. Sabouraud agars were incubated at 35 C for 72 hours and then at 25 C for up to 2 weeks. Plates were examined daily for detection of fungal growth. Colonies suggestive of fungal growth were evaluated by Giemsa and Calcofluor white stains and with slice culture to detect microscopic morphologic features and characteristic condition. Microscopic identification was supplemented with colony macroscopic characteristics (color, texture) and time to detection and was compared with standard mycology keys and textbooks.[7,8] Unusual isolates were sent to the Fungus Testing Laboratory (San Antonio, Texas, USA) for identification. Culture and identification techniques did not change during the study period (1990 through 2009).

Culture results were considered positive when there was growth of the same organism on 2 or more solid media at

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TABLE. Systemic Risk Factors of Patients with Endogenous Fungal Endophthalmitis

Risk Factor	No. of Cases	Risk Factor	No. of Cases
Recent hospitalization	35	Indwelling urinary catheter	7
Systemic surgery	16	Organ transplant	6
Cardiac disease (CAD, CABG) endocarditis	12	HIV/AIDS	3
Cancer	12	Total parenteral nutrition	3
Diabetes mellitus	11	Hemodialysis	2
Immunosuppressive therapy	11	Guillian-Barre syndrome	2
Respiratory disease (asthma, bronchitis, pneumonia)	10	Deep vein thrombosis	2
Gastrointestinal disease	9	Meningitis	2
Intravenous drug use	9	Prematurity	2
Intravenous line	9	End-stage liver disease	1

AIDS = acquired immunodeficiency syndrome; CABG = coronary artery bypass graft; CAD = coronary artery disease; HIV = human immunodeficiency virus.

All patients had at least 1 associated systemic medical condition. Twenty-four patients had 3 or more risk factors.

the inoculation site, or when the organism grew on 1 culture media and was noted on a stained smear (gram, Giemsa, or Gomori methenamine silver).[9] Treatment and management decisions were made by the individual treating physicians without a predefined study protocol.

RESULTS

• **DEMOGRAPHICS:** Study criteria were met in 51 patients (65 eyes). Of the 51 patients included in this study, 30 were men. The mean age was 51 years, with a range from 3 months to 92 years. Three patients were younger than 1 year of age. Follow-up ranged from 2 days to more than 15 years (median, 138 days). Fourteen patients had bilateral endogenous fungal endophthalmitis.

Time from onset of symptoms to presentation ranged from 0 to 60 days (mean, 13 days). No patients were identified through routine screening. The most common ocular symptoms were decreased vision (50 eyes; 77%), redness (32 eyes; 49%), pain (22 eyes; 34%), floaters (17 eyes; 26%), and photophobia (8 eyes; 12%). An initial diagnosis of endophthalmitis was made in 38 eyes (58%). The remaining cases were diagnosed with noninfectious uveitis. At initial evaluation, most eyes had diffuse anterior and posterior inflammation (46 eyes; 71%). Eighteen eyes (28%) had only focal posterior inflammation, and 1 eye (2%) had only focal anterior inflammation. Among 14 patients with bilateral endophthalmitis, 2 patients had diffuse inflammation in 1 eye and focal inflammation in the fellow eye.

All patients had at least one associated systemic medical condition (Table). Twenty-four patients (47%) had 3 or more risk factors. Thirty-five patients (69%) had been hospitalized in the past 6 months. Eight patients (16%) were hospitalized at the time of presentation. Sixteen patients (31%) in whom endogenous fungal endophthalmitis developed had not been hospitalized preceding presentation. The most common risk factor was nonocular surgery (16 patients; 31%). Fourteen patients were definitely immunosuppressed, with either immunosuppressive therapy (11 patients; 22%) or with HIV/AIDS (3 patients; 6%).

• **MICROBIOLOGIC DIAGNOSIS:** All 51 patients had positive intraocular culture results. The most common primary diagnostic procedure performed was vitrectomy in 37 eyes, which yielded positive culture results in 34 eyes (92%). Alternative primary diagnostic procedures included vitreous paracentesis in 16 (28%) of 57 eyes, yielding positive culture results in 7 eyes (44%) and aqueous paracentesis in 4 (7%) of 57 eyes, with 1 (25%) of 4 eyes yielding positive culture results. In 12 patients, initial aqueous or vitreous paracentesis culture results were negative, but subsequent vitrectomy specimens demonstrated positive culture results. Ultimately, a vitrectomy sample established or confirmed the diagnosis of endogenous fungal endophthalmitis in 46 eyes (81%). All 14 patients with bilateral disease had at least 1 eye yield positive intraocular culture results; in 6 of these 14 patients, intraocular culture results were obtained in both eyes, but culture results were positive from both eyes in only 1 patient.

Yeasts (38 patients; 75%) were more common than molds (13 patients; 25%). The most common causative yeast was *Candida albicans* (33 patients; 65%). Other yeasts were *Candida tropicalis* (n = 3) and *Cryptococcus neoformans* (n = 2). Molds identified included *Aspergillus fumigatus* (n = 6), *Aspergillus glaucus* (n = 2), *Fusarium oxysporum* (n = 2), *Aspergillus niger* (n = 1), *Aspergillus*

terreus (n = 1), and *Cladophialophora devriesii* (n = 1). The microbiologic results of the bilateral patients showed a spectrum that was not different from unilateral cases and were *Candida albicans* (n = 11), *Aspergillus fumigatus* (n = 2), *Candida tropicalis* (n = 1).

In addition to positive intraocular culture results, 11 patients (21%) had positive culture results from nonocular specimens. Of these, blood cultures demonstrated positive results in 6 patients (55%), urine cultures demonstrated positive results in 3 patients (27%), sputum cultures demonstrated positive results in 2 patients (18%), and cerebrospinal fluid demonstrated positive culture results in 1 patient (9%).

• **TREATMENTS AND OUTCOMES:** Initial treatment consisted of a combination of systemic and ocular treatment in 22 patients (43%). In patients undergoing both systemic and ocular treatment, ocular treatment consisted of intravitreal injection in 15 eyes and vitrectomy with or without lensectomy, intravitreal injection, or both in 12 eyes. Twenty-one eyes (35%) of 18 patients initially received only ocular treatment. Four of the 21 eyes underwent intravitreal injection alone. Seventeen eyes underwent vitrectomy with or without lensectomy, with or without intravitreal injection. One eye with predominantly anterior segment disease received intracameral amphotericin at the time of the vitrectomy.

Eleven patients (22%) initially were treated with only oral or intravenous antifungal agents without intraocular injections. Thirty-three patients had initial treatment with an oral agent (fluconazole, n = 28; ketoconazole, n = 4; or voriconazole, n = 1). Fifteen patients initially were treated with intravenous therapy (amphotericin B, n = 12; fluconazole, n = 2; itraconazole, n = 1).

During the course of management, 48 patients received systemic antifungal treatment: 28 patients with oral antifungal treatment alone; 9 with intravenous therapy alone, and 11 with a combination of oral and intravenous antifungals. Sixteen patients received more than 1 type of antifungal agent. Three patients had no systemic treatment at any point; however, 2 of these patients had limited follow-up (<2 days). In 2 bilateral cases 1 eye was managed with local and systemic therapy, whereas the fellow eye was managed with systemic therapy alone.

During the course of treatment, 50 eyes received intravitreal injections either at the time of surgery or in the clinic. The most common agent used was amphotericin B (5 μg/0.1 mL; 48 eyes). Three eyes were treated with voriconazole (50 μg/0.1 mL) intravitreally. Twenty-five eyes received only 1 dose of intravitreal amphotericin. Twenty-four eyes received more than 1 intravitreal injection (range, 2 to 7 injections; method, 2 injections). In these patients receiving serial injections, amphotericin was used in all but 1 patient. This 1 patient was infected with *C. albicans* and received 2 injections of voriconazole followed by 2 injections of amphotericin.

Fifty-nine of the 65 eyes (91%) included in the study underwent PPV during the treatment course. Thirty-eight of 59 eyes received an antifungal injection at the time of PPV. A diagnosis of endogenous fungal endophthalmitis had been confirmed with positive intraocular cultures before surgery in only 7 of these patients. Antifungal agents used were amphotericin B (36 eyes) and voriconazole (2 eyes).

Other indications for PPV included removal of inflammatory vitreous debris and repair of retinal detachments. Retinal detachment occurred in 17 eyes (29%). The causative organisms in these patients were as follows (*C. albicans*, n = 14; *C. tropicalis*, n = 1; *F. oxysporum*, n = 1; *A. fumigatus*, n = 1). Retinal detachment occurred in less than 1 week in 5 eyes (29%), and the remaining 12(71%) retinal detachments occurred after 1 week (range, 11 to 900 days). Retinal detachment developed in 7 eyes after 1 month. Retinal detachment developed in 8 of 14 patients (16 of 28 eyes) with bilateral endophthalmitis. Of the eyes with retinal detachment, 12 eyes (71%) had diffuse inflammation and 5 (29%) had focal inflammation. After surgical intervention, anatomic success was seen in 7 (42%) of 17 eyes.

Visual acuity was available for 47 patients (59 eyes) at their last follow-up examination. In the remaining 4 patients, visual acuity could not be assessed accurately because of the patient's young age or limited mental status. Visual acuity outcome of 20/200 or better was noted in 28 of 50 (56%) eyes with yeast and in 5 (33%) of 15 eyes with molds. Visual acuity of 20/50 or better was achieved in 21 (42%) of 50 eyes with yeast and in 1 (7%) of 15 eyes with molds. In patients with bilateral endophthalmitis, 17 (61%) of 28 eyes had a visual outcome of 20/200 or better, and 6 (21%) of 28 eyes had a visual outcome of 20/50 or better. All 3 eyes that underwent enucleation had positive culture results for *Aspergillus* species. Visual acuity in those eyes with retinal detachment was 20/200 or better in 5 (29%) of 17 eyes and 20/50 or better in 4 (24%) of 17 eyes.

DISCUSSION

THE CLINICAL FEATURES AND PRESENTATION OF ENDOGENOUS fungal endophthalmitis have been reported previously in multiple case reports and small clinical case series.[1–3,10–12] Few reviews have focused solely on endogenous fungal endophthalmitis. In addition, not all previously reported cases have been both microbiologically and clinically confirmed. To our knowledge, this study is the largest series of culture-proven endogenous fungal endophthalmitis.

Retinal detachment is not an uncommon complication after vitrectomy for endophthalmitis and is associated with poor visual outcomes.[13,14] The incidence of retinal detach-

ment in the Endophthalmitis Vitrectomy Study was 8%.[13] One large review of endogenous bacterial endophthalmitis reported a 2% rate of retinal detachment repair,[15] but there are no data available on incidence of retinal detachment after vitrectomy for endogenous fungal endophthalmitis. The overall incidence of retinal detachment in this series was 17 (29%) eyes. In 7 eyes, retinal detachment developed after 1 month after PPV, suggesting contraction of the peripheral vitreous and consequent retinal break as a cause. After surgical intervention, anatomic success was seen in 7 (42%) of 17 eyes. In 4 eyes (24%), visual acuity of 20/50 or better was achieved.

The vast majority of patients underwent a pars plana vitrectomy during the course of follow-up. The goal of surgical intervention is to obtain an adequate sample and to clear vitreous opacities to restore vision. In this series of culture-positive cases only, vitrectomy was more likely to yield positive culture results as a primary diagnostic method than anterior chamber tap or vitreous tap without vitrectomy. Vitrectomy yielded positive culture results in 92% of eyes when this method was used as the initial diagnostic procedure. Alternative initial diagnostic procedures included anterior chamber paracentesis and vitreous tap without vitrectomy, which yielded positive culture results in 25% and 44% of eyes, respectively. Previously published reports also have suggested that a vitrectomy sample is more likely to yield positive culture results compared with vitreous tap.[10] Because endogenous fungal endophthalmitis generally begins with seeding of the choroid, it has been suggested that vitreous tap may not adequately sample the vitreous cavity, particularly with mold infection.[16]

In the current series, the most common causative organism isolated in culture-proven endogenous fungal endophthalmitis was *C. albicans* (33 patients; 65%). In 13 patients, molds were isolated. This distribution of fungal species agrees with the results of prior series.[3,17] In this series, intravitreal amphotericin was the most common antifungal used. Of the 3 eyes that were enucleated, all 3 had positive culture results for *Aspergillus*. As reported in prior studies, visual outcomes were worse with molds than with yeasts.[2,3] It has been suggested that molds tend to cause more infiltrating infection and are less responsive to current antifungal therapy.[16]

Candida endogenous endophthalmitis may present as progressive uveitis, which has been reported in as many as 50% of endogenous fungal endophthalmitis cases in some series.[6,12] In the present series, the clinical diagnosis of endogenous fungal endophthalmitis was established first in 58% of patients by means of positive culture results. This finding underscores the importance of obtaining microbiologic testing and maintaining a high index of clinical suspicion, particularly in patients with a history of recent hospitalization, abdominal surgery, intravenous drug abuse, or immunocompromise. In patients with worsening posterior segment inflammation without an established cause, diagnostic procedures can establish the correct cause and subsequently can support the need for appropriate therapy. However, no cases of endogenous fungal endophthalmitis were identified through routine screening of septic fungemia patients in this series. Ocular screening in patients with candidemia is recommended for children, critically ill patients, and patients with impaired consciousness or ocular symptoms.[18]

Following the observations made in the current study, we recommend a high index of clinical suspicion for endogenous infectious uveitis in patients with risk factors as identified (Table) and clinical signs such as diffuse vitreitis, chorioretinal inflammatory lesions with focal vitreous inflammation, or subretinal chorioretinal lesions. In such patients, a diagnostic vitrectomy should be considered. Based on clinical findings and culture results, appropriate intravitreal therapy can be given. Oral antifungal agents also are considered, typically fluconazole. Repeat intravitreal injections once or twice weekly may be required until the infection subsides. Patients should be followed up for the possibility of developing retinal detachment.

This study has many limitations, including its retrospective design, lack of uniform protocol for diagnosis or treatment, limited and variable follow-up, and limited use of newer antifungal treatments, such as voriconazole. Despite these shortcomings, this series confirms prior reports on endogenous fungal endophthalmitis, that there is a predominance of *Candida* cases, poor visual outcomes among mold cases, and frequent retinal detachment (29%) in involved eyes. In addition, this series documents that vitrectomy is more likely to yield positive diagnostic culture results than anterior chamber or vitreous tap without vitrectomy. Finally, this series documents final visual acuity of 20/50 or better in 24% of eyes with retinal detachment associated with endogenous fungal endophthalmitis.

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Biosketch

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