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The role of pars plana vitrectomy in the management of fungal endogenous endophthalmitis

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Abstract

Purpose: To identify the causative microorganism of fungal endogenous endophthalmitis in our tertiary referral uveitis center and review the therapeutic role of pars plana vitrectomy in patients with fungal endogenous endophthalmitis.

Methods: Seven eyes of six cases were identified as fungal endogenous endophthalmitis through positive cultures of ocular fluids and clinical presentations. The final anatomical and functional results were evaluated.

Results: Four women (66.7%) and two men (33.3%) underwent vitrectomy. Control of infection was achieved early on in all cases. *Candida* (71.4%) and *Aspergillus* (28.6%) species were identified as causative fungi in patients with fungal endogenous endophthalmitis. Two patients were reoperated due to reinfection and retinal detachment, respectively. Visual acuity improved in six eyes (85.7%) and worsened in one eye (14.3%). At the final examination, the retina was flat in all cases. No eye developed phthisis bulbi.

Conclusion: *Candida* species are the most common causative organisms of fungal endogenous endophthalmitis in this study. Pars plana vitrectomy in fungal endogenous endophthalmitis may enhance the treatment of infection by removing fungal elements in the vitreous and aid in diagnosis. Vitrectomy may also be an important tool in the management of vision-threatening post-infectious sequelae such as retinal detachment and reinfections.

Keywords

Endogenous endophthalmitis, fungal endophthalmitis, infectious, surgery, vitrectomy

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Introduction

Endogenous endophthalmitis (EE) is an uncommon, progressive, and potentially blinding intraocular infection. EE comprises 2%–15% of all cases of endophthalmitis.[1,2] EE or intraocular infection from hematogenous spread from the remote primary source can occur with bacterial, fungal, viral, and parasitic sources.[3] Fungal endogenous endophthalmitis (FEE) is a serious ocular condition associated with potentially devastating visual outcomes, which originates from hematogenous dissemination of a fungal organism.[4] Most commonly, FEE is associated with *Candida* or *Aspergillus* species.[5–7] Yeasts account for 75% of cases of FEE and have a poor prognosis, with 25% of patients developing a retinal detachment (RD).[8] Most patients with FEE have one or more predisposing systemic conditions and risk factors, such as diabetes mellitus (DM), prolonged recent hospitalization, iatrogenic immunosuppression, whole organ transplantation, malignancy, indwelling catheters, intravenous drug abuse (IVDA), liver disease, renal failure, recent major surgeries, hyperalimentation, acquired immune deficiency syndrome (AIDS), endocarditis, urinary tract infections (UTIs), and dental procedures.[5,6,8–12] FEE may occur rarely in healthy, immunocompetent patients with no risk factors or who have only an infected toenail as the source.[13]

FEE is frequently a diagnostic dilemma for clinicians with significant vision-threatening consequences for patients.[14] Standard regimens for FEE treatment were systemic antifungals, intravitreal antifungal injections, and pars plana vitrectomy (PPV).[15] Nonetheless, due to the

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lack of the large series and prospective studies, the efficiency of PPV in FEE is still debatable. In this study, we aimed to identify the causative microorganism of FEE and report the results of PPV with adjuvant intravitreal amphotericin B and systemic antifungal therapy management in patients with FEE who were vitreous culture proven in our tertiary care referral uveitis center.

Methods

A retrospective review was conducted of all cases who were intraocular fluid culture proven with FEE at our tertiary referral hospital. From December 2013 to March 2017, seven eyes of six FEE patients were treated in our institute with PPV. The study protocol was approved by the local Institutional Ethics Board and conducted according to the tenets of the Declaration of Helsinki. The data collected from the medical records included demographic features such as age, gender, clinical presentations, predisposing factors, causative fungal pathogens, and visual outcomes. The diagnosis of FEE was attributed by the following standards (unilateral/bilateral): anterior uveitis and/or vitritis and presence of retinitis foci, existence of an extraocular source of infection, and positive microbiologic cultures of any of the specimens such as blood, urine, and indwelling catheter. Precise inclusion criterion was that ocular cultures have to be positive for fungus and have no coexistent ocular surgery or trauma. Despite the identification of FEE in the examination findings, if the ocular culture was negative for fungi, such patients were excluded from this study, even if one of the extraocular sample cultures was positive. The patient who had a history of eye trauma or intraocular surgery was also excluded. A history of predisposing factors, including chronic illnesses, DM, cancer/chemotherapy history, radiation therapy, any treatment with immunosuppressive medicines, renal failure, indwelling catheters, AIDS, liver disease, IVDA, alcoholism, dental procedures, organ transplantation, endocarditis, total parenteral nutrition, blood transfusion, UTI, recent surgeries, and any infection in the whole body was noted. Complete ophthalmologic examination included best corrected visual acuity (VA) testing, slit-lamp biomicroscopy, tonometry, and fundoscopy performed during the ophthalmic visits. If a patient was in intensive care unit (ICU), a dilated fundus examination of both eyes was performed at the bedside of the patient. B-scan ultrasound was performed if the media is not clear. All cases had undergone vitreous tap and intravitreal antimicrobial agent injection at the same time before the PPV at the first suitable time. Major ocular specimens were obtained for cultures via PPV. When the general health condition of the patients was convenient, a standard three-port 23G PPV was performed. All the surgeries were implemented by the same surgeon (H.C.). During the PPV, to avoid a diluted vitreous sample, the aspiration line was connected to a 5-mL disposable syringe. While the surgeon was cutting and aspirating the vitreous, the assistant applied delicate suction with the syringe. During this process, the infusion line was kept as closed as possible. Three samples were acquired with this procedure. During the surgery, these samples were sent for microbiological analyses. Lensectomy was carried out if needed. The inflamatuar membranes were peeled from retinal surfaces with more attention and on top of the ciliary bodies. Multiple air-to-fluid and fluid-to-air exchanges flushed out and cleared the vitreous cavity. In case of the presence of retinal tears, laser photocoagulation was carried out. After this procedure, 1300 cSt silicon oil was injected into all of the eyes. Intravitreal amphotericin B (1.25 μg/0.1 mL) was administered at the end of the surgery into the vitreous cavity. Finally, container of the vitrectomy machine was also sent to the microbiology department in an intact condition to preclude contamination for the microbiological assessment. Systemic and intravitreal antimicrobial therapies were noted.

VA was assessed in European decimals (with a Snellen chart) and then converted to the logarithm of the minimum angle of resolution (logMAR) for computing. NCSS (Number Cruncher Statistical System) 2007 Statistical Software (NCSS, LLC, Kaysville, UT, USA) program was used for the statistical analysis. The following scales were applied to logMAR values for low vision states: counting fingers (CF), 1.9; hand motion (HM), 2.3; and light perception (LP), 2.7. During the evaluation of the study data, calculation of descriptive statistical methods (mean, standard deviation, median, frequency, and rate) was used. Wilcoxon signed-rank test was applied for the intragroup comparisons of VA of the initial and the last examination without normal distribution. Significance was defined as $p < 0.05$.

Results

Seven eyes of six patients with fungal EE were included in the study. Four patients (66.7%) were women and two (33.3%) were men. The mean age was 55.33 ± 23.08 years (range: 22–78 years). Of the patients, one (16.7%) had bilateral and five (83.3%) had unilateral ocular involvement (two right and three left eyes). The most common presenting symptom was visual disturbance (n = 4, 66.7%). Two patients (33.3%) had multiple complaints such as visual disturbance, ocular pain, and conjunctival hyperemia. Of the cases, three (50.0%) received ICU treatment. Time delay until PPV surgery was measured as mean 10.71 ± 8.58 days, median 7 days (min–max: 4–25), respectively. The mean duration of follow-up was 25.50 ± 18.47 months (range: 12–39). Patients' general characteristics are summarized in Table 1.

The most common predisposing systemic diseases in patients with FEE were DM (n = 3, 50.0% (two of the patients had UTI; in these two patients who had UTI, one

Table 1. General characteristics of patients with fungal endogenous endophthalmitis (n = 6).

n = 6		
Age (years)	Min–max (median)	22–78 (58)
	Mean ± SD	55.33 ± 23.08
Gender, n (%)	Woman	4 (66.7)
	Man	2 (33.3)
Laterality, n (%)	Right	2 (33.3)
	Left	3 (50.0)
	Bilateral	1 (16.7)
Initial complaint, n (%)	Visual disturbance	4 (66.7)
	Visual disturbance + pain + redness	2 (33.3)
Presentation, n (%)	Outpatient	3 (50.0)
	ICU	3 (50.0)
Follow-up time (months)	Min–max (median)	12–39 (24)
	Mean ± SD	25.50 ± 11.38

SD: standard deviation; ICU: Intensive care unit.

Table 2. Diagnosis, type of fungi, predisposing factors, and systemic antifungal treatments.

n = 6		
Culture source, n (%)	Blood	5 (83.3)
	Blood + urine	1 (16.7)
Type of fungus[a], n (%)	Yeast	5 (83.3)
	Mold	1 (16.7)
Medical/surgical history, n (%)	Malignancy	1 (16.7)
	DM	1 (16.7)
	DM + UTI	1 (16.7)
	DM + UTI + catheterization	1 (16.7)
	Intestinal surgery	1 (16.7)
	Abdominal surgery	1 (16.7)
Systemic antifungal therapy, n (%)	Fluconazole	2 (33.3)
	Amphotericin B	1 (16.7)
	Amphotericin B + cefuroxime	1 (16.7)
	Fluconazole + vancomycin + caspofungin	2 (33.3)

DM: diabetes mellitus; UTI: urinary tract infection.
[a]Isolated from blood and urine samples.

had an indwelling catheter as well)), malignancy (n = 1, 16.7%), and other medical conditions (n = 2, 33.3%; abdominal surgery and gastrointestinal surgery). Vitreous specimens and blood samples were positive in all patients (n = 6, 100%). In one case (16.7%), all samples (vitreous, blood, and urine) were detected as positive. Systemic treatment of FEE patients included systemic antifungal therapy (amphotericin B, fluconazol, and caspofungin) and systemic prophylactic antibacterial therapy (in the ICU; cefuroxim and vancomycin; Table 2). Systemic antifungal treatment was continued until blood cultures were detected as negative. The systemic antifungal therapy course was followed up by the infectious disease department.

Among fungal isolates from vitreous samples, five (71.4%) were yeast (four *Candida albicans* and one *Candida glabrata*) and two (28.6%) were mold (*Aspergillosis*). In the blood and urine samples, *Staphylococcus aureus, Klebsiella pneumoniae*, and *Acinetobacter baumannii* were identified. Five (71.4%) eyes experienced no surgical complications. Two eyes had post-surgical complications (one (14.3%) had RD and one (14.3%) had recurrent infection; Table 3).

VA of all eyes was available at the initial and last follow-up examinations. VA improved in six eyes (85.7%) and worsened in one eye (14.3%). The logMAR VA values at the presentation and last follow-up examination (last follow-up examination was accepted as between 12 and 18 months of follow-up period for the statistical evaluation) were 1.80 ± 0.41 and 1.11 ± 0.74, respectively. The average increase in VA of 38.92% ± 36.75% was not statistically significant (Wilcoxon signed-rank test, $p = 0.063$; $p > 0.05$) (Table 4 and Figure 1) due to the small number of cases. At the initial slit-lamp examination, mild anterior

chamber reaction was detected in all cases. Intraocular pressure measurements were within normal limits. All cases had vitreous reaction. In those patients who had a visible retina during retinal examination, a string of pearls configuration was observed. At the final examination, anterior chamber reaction was controlled for all patients. Vitreous cavities were clean. All retinas were flat.

Discussion

FEE is a rare intraocular infection that can result in devastating ocular complications. Although there are a large number of reports that evaluate the effective treatment in small and large case series, the comparative rarity of the disease, distinction of the predisposing factors, variableness of the causative microorganisms, and the variety of antifungal agents administered make this condition difficult to study with randomized controlled trials. In this retrospective case series of six patients, we aim to identify the causative microorganism of FEE in our tertiary referral uveitis center and to report the outcomes of the therapeutic effect of PPV in the patients with ocular culture-proven FEE. The cases were evaluated in terms of causative pathogenic microorganisms, underlying systemic diseases, visual outcomes, and surgical complications.

Due to the insidious nature of the symptoms, diagnosis of FEE can be difficult. In addition, the findings of FEE may imitate other eye ailments. In this situation, if a diagnostic challenge is encountered, the infectious disease may worsen because of the diagnostic delay or misdiagnosis. In this study, as part of the diagnosis of FEE, a vitreous tap was performed on all of the eyes before performing PPV. However, except for two eyes, microbiological assessments were negative for the other samples. According to the microbiological report, due to the small sample size of the vitreous tap material, causative microorganisms could not be detected. Subsequently, all PPV specimens (n = 7) demonstrated positive results for the fungi. PPV yielded more material for the microbiologic tests for all patients. In one study, 65 eyes of 51 patients with FEE had positive culture results. PPV was performed on 37 eyes, which yielded positive culture results in 34 eyes (92%). Vitreous tap was performed 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%) yielding positive culture results. In 12 patients, initial aqueous or vitreous paracentesis culture results were negative, but subsequent vitrectomy specimens showed positive culture results. These cases initially carried an incorrect diagnosis of noninfectious uveitis.[8] In another case series of patients with FEE, 55% of vitreous specimens in 20 patients were negative. These patients subsequently underwent PPV and all vitreous biopsies were positive for fungi.[16] In our opinion, thanks to the benefit of increased sample volume, vitrectomy can play an important role in the diagnosis of FEE.

In this study, of the fungal isolates from the vitreous samples, five (71.4%) were yeast (four *C. albicans* and one *C. glabrata*) and two (28.6%) were mold (*Aspergillus fumigatus*). Sridhar et al.[10] revealed that the risks of complications in FEE are substantial and related to the virulence of the organism. They found that one eye had an RD. This patient also had *A. fumigatus* and a delayed diagnosis of 1 month. They emphasized that these two factors are associated with poorer outcomes.[10,17] Birnbaum and Gupta reported six cases with FEE who underwent PPV. They observed RD in one eye which was infected with *A. fumigates*.[14] In our study, we reported two FEE patients who were infected with *A. fumigatus*. However, these cases had good visual outcomes and experienced no complications. Two cases had post-surgical complications (one (14.3%) had RD and one (14.3%) had recurrent infection), and these cases were *C. albicans* culture proven. In our opinion, according to these reports, *A. fumigatus* may not be

Table 3. Distribution of the organisms and surgical complications.

n = 7		
Type of fungus, n (%)	Yeast	5 (71.4)
	Mold	2 (28.6)
Identified microorganism[a], n (%)	*C. albicans*	4 (57.1)
	Aspergillus	2 (28.6)
	C. glabrata	1 (14.3)
Complication, n (%)	Recurrent infection	1 (14.3)
	Retinal detachment	1 (14.3)
	No	5 (71.4)

[a]Isolated from vitreous samples.

Table 4. Comparison of logMAR visual outcomes of initial and final examinations of patients with fungal endogenous endophthalmitis (Wilcoxon signed-rank test).

	LogMAR visual acuity (n = 7)			p
	Initial examination	Final examination	Change of initial and final visual acuity (%)	
Min/max (median)	1/2.3 (1.9)	0.4/2.7 (1.0)	−42.11/63.16 (50.0)	0.063
Mean ± SD	1.80 ± 0.41	1.11 ± 0.74	38.92 ± 36.75	

SD: standard deviation.

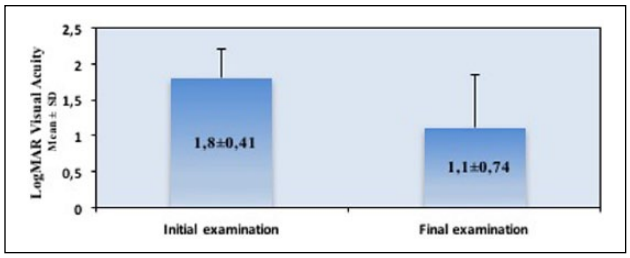

Figure 1. LogMAR visual acuity changes at the first and the last examination.

the reason for the poor prognostic factor in every instance of FEE.

The appropriate time to perform the surgery in FEE is still controversial. While some researchers recommend PPV in FEE at presentation, others have reported mixed results as to the benefit on long-term visual outcomes.[18–21] Vitrectomy surgery was classified as "early" if surgery was performed within the first week of the diagnosis of suspected FEE, and otherwise as "late" in the literature.[22] In our study, five patients underwent early vitrectomy. We could not compare early and late vitrectomy groups statistically due to the small number of cases. Two patients had complication in this case series. The patient who had reinfection complication underwent late vitrectomy (at the 25th day). However, the other who had RD had immediate vitrectomy (at the 7th day). Sallam et al.[22] reported 36 patients who had endogenous candida endophthalmitis. Early vitrectomy was undertaken in 26 of 44 eyes (59.0%) within the first week of presentation. Early PPV was not possible in 18 of 44 eyes (41.0%) due to their systemic diseases. In this study, they emphasized that there was a significant association between early vitrectomy and a decreased incidence of developing RD.[22] Birnbaum and Gupta[14] reported six cases of FEE. All cases were managed with early PPV within 24 h and their diagnostic delay averaged 7.5 days (0–30 days). They showed that an early PPV may improve visual outcomes.[14] Nevertheless, Cho et al.[23] showed that the timing of PPV in EE (defined as immediate vs delayed) was not associated with visual outcome ($p = 0.859$). Zhang et al.[20] have reported better visual outcomes in cases that underwent early vitrectomy in EE.

In this study, a 38.9% ± 36.7% increase was gained in VA at the last visit. VA of 20/200 or better was achieved in six (85.7%) of the seven eyes. Christmas and Smiddy showed that six eyes of five patients with advanced EE were treated with fluconazole and PPV. All patients had improvement in vision, with five of six eyes achieving a final VA of 20/40 or better.[24] In a report, 11 of 29 (38.0%) operated eyes achieved a VA of 20/200 or better.[16] In a review study, 13 of 29 (44%) vitrectomized eyes showed a VA of 20/200 or better.[17] In this study, we achieved a better rate of increase in visual outcomes (85.7%) than these other studies. Nonetheless, our sample size was more limited than the others, and thus the average increase in VA was not statistically significant due to the small number of cases. This improvement, however, seems to be important. It is predicted that this gain will be statistically significant in larger series. Birnbaum and Gupta[14] reported that a VA of 20/200 or better was achieved in five of six eyes (83.3%). These results might be presumed compatible with ours. In our opinion, in addition to helping clinicians to diagnose the etiology of the infection, PPV decreases the toxic infectious and inflammatory burden to the macula from the vitreous. In addition, vitrectomy can clear the eye of opaque media. Therefore, because of these many beneficial attributes, PPV may contribute to improving the VA.

Amphotericin B has been a mainstay in the treatment of fungal infections since its development and use in the late 1950s.[25] However, intravitreal use of amphotericin B is not without its own set of risks due to concern for retinal toxicity and necrosis with inadvertent dilution error or if used in an air- or oil-filled eye.[26,27] In this study, we administered intravitreal amphotericin B, a quarter dose of the usual intravitreal dosage (1.25 μg/0.1 mL), in the silicon oil–filled eyes at the end of the surgery. We observed no toxic effect of the use of intravitreal amphotericin B in the vitrectomized eyes at this dosage. In our opinion, if an intravitreal antifungal drug is used at an appropriate non-toxic dosage, PPV can improve the diffusion of antifungal agents into the vitreous cavity, retina, and choroid, and thus this can be an advantage of vitrectomy also.

Most of the case series accepted all body sample culture results as an inclusion criterion because in large series of EE blood cultures were more likely to be positive than vitreous.[28–30] For instance, Paulus et al. reported that the inclusion criterion in their study was blood culture positivity. This study included no ocular culture-proven specimens.[3] In our study, we excluded no vitreous sample-proven cases because, as these cases may have multiple organisms (fungi, bacteria) in the other body samples (such as blood and urine), we aimed to escape the bias as to which organism was causative for EE. Even if this inclusion criterion reduced our sample size, we believe that this condition was more reliable than the other non-vitreous sample-proven studies.

There are no randomized controlled trials to evaluate the efficacy of posterior vitrectomy to treat FEE. The only evidence verifying its benefits originate from the results of case reports and case series of FEE. Smaller case series have reported more favorable VA results.[31] In our opinion, until multicenter, randomized, controlled studies are performed, case series will maintain their importance and value. In this study, we aimed to share the results of our surgical experience of this rare disease with a poor prognosis. *Candida* species were the most causative fungus type in our patients with FEE. The limitations of this case series were its retrospective design and small sample size. In conclusion, we believed that PPV was the effective

diagnostic approach for the FEE cases. We hope that this report will lead to multicenter, prospective studies in the future.

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Declaration of conflicting interests

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