ENDOGENOUS ENDOPHTHALMITIS ASSOCIATED WITH INTRAVENOUS DRUG ABUSE

Seven-Year Experience at a Tertiary Referral Center

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Purpose: Intravenous drug use (IVDU) is a known risk factor for endogenous endophthalmitis. Endogenous fungal endophthalmitis (EFE) is emerging as a common problem among this community. We describe the management and visual outcomes of acute IVDU-associated EFE.

Methods: A prospective consecutive case series of 19 patients presenting with presumed acute IVDU-associated EFE from 2001 to 2007 to the Royal Victorian Eye and Ear Hospital was included. All data were collected in a standardized manner. Outcome measures included visual acuity, microbial profiles, and vitrectomy rate.

Results: Nineteen cases of IVDU-associated EFE were identified. Eight of these (42%) were men, and the mean age was 32.7 years (SD $\pm$ 8.0 years). Presenting visual acuity ranged from 6/6 to perception of light, with 58% having a visual acuity of 6/48 or less at presentation. Thirteen (68.4%) were culture positive with all cultures identifying *Candida* species, and 52.7% underwent vitrectomy. Fifty percent of subjects overall achieved a final visual acuity of 6/18 or better. Men demonstrated improved visual acuity when compared with women ($P = 0.04$). Age had no effect on final acuity.

Conclusion: Intravenous drug use is a significant risk factor for developing EFE. Good visual outcomes can be achieved with early treatment, often with intravitreal therapy alone.

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Endogenous endophthalmitis is an intraocular infection in which the causative organism reaches the eye through disseminated hematogenous spread.^{1,2} It is estimated that approximately 2 to 10% of all endophthalmitis cases are endogenous. The majority of cases are associated with an immunocompromised state, debilitating disease, invasive procedures, malignancy, and intravenous drug use (IVDU).^{3,4}

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Endogenous fungal endophthalmitis (EFE) is a known complication of disseminated fungal infections and is potentially blinding.^{1,2} It is more prevalent than previously believed, especially in developing countries.⁵ Most reported cases of EFE occur in immunocompromised hosts. The frequency of EFE among patients with known systemic fungal infection has been reported to vary between 2 and 45%.³ The number of people living in a prolonged immunocompromised state is increasing. Advances in medical therapy and diagnosis have led to increased incidence of this condition. In clinical practice, many patients with EFE are misdiagnosed or diagnosed late with a resultant delay in treatment and poor visual prognosis.¹

vitreotomy or tap and injection were compared by using chi-square tests or Fisher exact test of chi-square depending on the cell frequencies. Visual results were obtained from the difference in Snellen visual acuity pretreatment and posttreatment and categorized into 3 groups: 1) gain of 2 lines or more; 2) no change; and 3) loss of 1 line or more. Fisher exact test of chi-square was used if any outcome frequencies were less than five. Pretreatment and posttreatment visual acuities were compared for the total sample, for gender, and for age group (age below or equal to 35 versus above 35 years) by using paired sample *t*-test. All analyses were performed in SPSS version 16.0.1 (SPSS, Inc, Chicago, IL), and comparisons were regarded as statistically significant for $P \leq 0.05$.

Results

Nineteen patients with a positive history of IVDU diagnosed with EFE over the 7-year study period were included in this study. Five patients were on buprenorphine treatment. The mean age was 32.7 years ($SD \pm 8.0$ years), and 8 were men (42%). Presenting Snellen visual acuity ranged from 6/6 to perception of light, with a mean acuity of 6/48. No fundal view was possible in 11 of 19 patients on presentation. The mean time from onset of symptoms to presentation was 2.5 days (range 1–13 days). The clinical characteristics are listed in Table 1.

Of the 19 patients, 13 were culture positive (68.4%). A positive culture was obtained on vitreous biopsy (tap) alone in 6 of 9 patients (66.7%). Repeat aspiration biopsy in those initially negative did not increase this yield. A 70% culture-positive rate in those undergoing formal vitrectomy (7 of 10 patients) was found ($P = 0.63$). All positive cultures isolated *Candida* species (Table 1).

Ten of 19 patients (52.7%) underwent formal pars plana vitrectomy, 7 on initial presentation due to the severity of vitreous inflammation and retinitis, with the remainder performed for deteriorating disease. When secondary vitrectomy for clinical deterioration was performed, there was no additional isolates identified. The fundus was visible in 30% of those undergoing initial vitrectomy (Table 2). In nine cases, initial needle biopsy was performed due to ocular signs of mild to moderate inflammation. The fundus was visible on presentation in 56% of those managed with tap and injection. Repeat injection was performed in three cases, due to an indeterminate clinical response to the initial injection. Intravitreal amphotericin ($5 \mu\text{g}/0.1 \text{ mL}$) was administered in all cases, with the addition of antibiotics in initially inconclusive cases (31.5%). In these patients, a definite history of

Intravenous drug use is a known risk factor for EFE. Heroin users are a high-risk group for disseminated candidiasis.⁶ Recently, oral substitutes for heroin, including oral methadone and high-dose sublingual buprenorphine tablets, have proven effective in the management of opioid addiction.⁷ Reports have highlighted the potential for misuse and diversion of these substitutes, with resultant ocular complications from systemic administration.^{8,9}

Few large case series have documented EFE after IVDU. The purpose of this article was to document the incidence, presentation, visual outcome, and microbiologic profile of EFE after IVDU presenting to a single tertiary referral center. The role of vitrectomy in management is outlined.

Material and Methods

A prospective data collection of all patients presenting with a clinical diagnosis of presumed EFE to The Royal Victorian Eye and Ear Hospital, Melbourne, Australia, between 2001 and 2007 was conducted. Inclusion criteria were evidence of endophthalmitis in either eye, defined as the presence of anterior/posterior segment inflammation on ophthalmic examination, vitritis, or characteristic fundal lesions temporally unrelated to a potential exogenous cause and a history of IVDU. The demographic data collected included age, sex, and predisposing risk factors and clinical data including clinical examination, investigations performed, microbiologic profiles, treatment, and final visual acuity at last follow-up.

All microbiologic analyses were carried out at the microbiology laboratory at St. Vincent's Hospital, Melbourne. Diagnosis was based on microscopy (gram staining) and culture positivity. For microbial analysis, anterior chamber aqueous samples and posterior cavity vitreous samples were taken. Samples were obtained in accordance with hospital protocols and under aseptic technique. Aqueous samples were obtained through an anterior chamber paracentesis attached to a 1-mL insulin syringe, and vitreous samples were obtained through an aspirated tap of the posterior segment or during formal vitrectomy. All samples were processed without delay on culture media selected by the microbiologist based on the likely pathogen. The research was conducted in accordance with the Declaration of Helsinki and local ethics committee guidelines.

Statistical Analysis

Culture positivity based on method of sampling, visual results based on method of treatment, and fundal view status at presentation and about the association of

Table 1. Clinical Characteristics of Patients

Case	Sex	Age	Fungus	Predisposing risk factor	Vitrectomy	Initial VA	Final VA
1	M	30	<i>Candida albicans</i>	IVDU	Y	6/60	6/60
2	M	29	<i>C. albicans</i>	IVDU	Y	6/36	6/18
3	F	34	<i>C. albicans</i>	IVDU	N	HM	6/36
4	F	31	<i>C. albicans</i>	IVDU	Y	6/48	6/9
5	F	43	<i>C. albicans</i>	IVDU	N	2/60	6/12
6	F	29	<i>C. albicans</i>	IVDU	N	HM	2/60
7	F	59	<i>C. albicans</i>	IVDU	N	PL	HM
8	M	26	<i>Candida tropicalis</i>	IVDU	N	HM	6/60
9	M	37	<i>C. tropicalis</i>	IVDU	Y	CF	HM
10	M	37	<i>Candida dubliniensis</i>	IVDU	Y	6/6	6/12
11	M	33	<i>C. dubliniensis</i>	IVDU	Y	6/36	6/9
12	M	28	<i>C. dubliniensis</i>	IVDU	N	6/36	6/6
13	F	36	<i>C. dubliniensis</i>	IVDU	Y	6/60	CF
14	F	33	No growth	IVDU	N	HM	2/60
15	M	32	No growth	IVDU	Y	HM	2/60
16	F	22	No growth	IVDU	Y	6/9	6/6
17	F	31	No growth	IVDU	N	6/6	LtF
18	M	29	No growth	IVDU	N	6/18	6/9
19	M	22	No growth	IVDU	Y	6/24	6/12

CF, counting fingers; F, female; HM, hand motions; LtF, lost to follow-up; M, male; N, no; PL, perception of light; VA, visual acuity; Y, yes.

IVDU was not volunteered until 48 hours post admission. The most common additional intravitreal antibiotics used were a combination of ceftazidime (2.25 mg/0.1 mL) and vancomycin (1 mg/mL). All patients in this series were placed on systemic oral antifungal therapy.

Final Snellen visual acuities were available for 18 of 19 patients and ranged from 6/6 to hand motion with a mean visual acuity of 6/36. Fifteen of 18 patients (83.3%) achieved a final visual acuity of $\geq 2/60$ (Table 1). In those managed with biopsy and intravitreal therapy alone, from an initial mean visual acuity of 6/60, a mean final visual acuity of 6/36 was recorded, with 44.5% achieving $\geq 6/18$. Repeat injection did not confer a worse visual outcome. In those requiring pars plana vitrectomy, from a mean presenting visual acuity of 6/36, a mean final vision of 6/24 was recorded with 60% achieving $\geq 6/18$. Overall, 50% of subjects (9 of 18) achieved

a final visual acuity of 6/18 or better. Culture positivity was not correlated with a worse visual prognosis.

Male patients demonstrated improved visual outcome in comparison to female subjects ($P = 0.04$). A younger age profile of ≤ 35 years did not confer a better visual prognosis (Table 3).

Discussion

Endogenous fungal endophthalmitis is a rare entity, which can occur at any age and often results in severe visual loss.^{1,2,5,10} Bilateral involvement is often seen, particularly in those with underlying medical conditions such as immunosuppressive disorders including human immunodeficiency virus, malignancies, and associated chemotherapy and immunocompromising disease such as diabetes mellitus, renal failure, and intravenous drug abuse.

Table 2. Culture Positivity Based on Method of Sampling and Visual Results Based on Method of Treatment and Fundal View Status of 19 Patients

	Vitrectomy (n = 10)	Tap/inject (n = 9)	P*
Culture positivity (%)			
Culture positive	7 (70)	6 (66.7)	0.63
No growth	3 (30)	3 (33.3)	
Visual results (1 patient lost to follow-up), %			
Lost ≥ 1 line	3 (30)	0	0.13
No change	1 (10)	0	
Gain ≥ 2 lines	6 (60)	8 (100)	
Fundal view (%)			
Present	3 (30)	5 (56)	0.26
Absent	7 (70)	4 (44)	

*P from the Fisher exact test.

Table 3. Gender and Age Effect on Change in Visual Acuity After Treatment

P	Posttreatment		Pretreatment		P
	VA	VA	VA	VA	
Gender effect					
Male (n = 10)	6/24 (mean)	6/48 (mean)	6/48 (mean)	6/60 (mean)	
Female (n = 9)	6/48 (mean)	6/60 (mean)	6/60 (mean)	6/60 (mean)	
Age effect					
Age ≤ 35 years (n = 14)	6/36 (mean)	6/48 (mean)	6/48 (mean)	6/60 (mean)	
Age > 35 years (n = 5)	6/36 (mean)	6/48 (mean)	6/60 (mean)	6/60 (mean)	
					P < 0.05.

70%, respectively, which was not improved with repeat biopsy. Shen and Xu in their series of 25 patients demonstrated a negative culture rate of 55% on initial ocular sampling (both anterior chamber and posterior segment samples). However, although initial biopsy was negative, cultures or smears obtained by formal vitrectomy were subsequently positive in their series.¹⁵ They postulated that more adequate sampling could be obtained by vitrectomy and biopsy near the retinal surface where, based on pathogenesis of disease, the highest concentrations of potential organisms are often found.

Polymerase chain reaction (PCR) is emerging as the diagnostic tool of choice for identifying pathologic microbes in infective endophthalmitis, whether bacterial or fungal. Sowmya and Madhavan demonstrated a 100% identification rates using PCR in infectious endophthalmitis in their series. By comparison, using standard culture techniques, isolates were identified in only 37.5% in the same cohort.¹⁶ There was no difference in detection rates by PCR between aqueous and vitreous samples. Furthermore, recent studies have shown that real-time PCR has the capability of identifying the offending pathogen in only 90 minutes, offering a potential future rapid and accurate diagnostic tool in this potentially sight-threatening condition.^{17,18} In our series, PCR was not used.

Endogenous fungal endophthalmitis represents a diagnostic and treatment challenge. Some studies have reported misdiagnosis and delayed diagnosis rates for *Candida* endophthalmitis approaching 50%.¹⁹ In our series, all patients were diagnosed early upon presentation due to the associated risk factor of IVDU and the suspicion for fungal septicemia. Once diagnosis is made, prompt treatment is indicated. Interestingly, in our series, 52.7% of subjects were managed with vitrectomy. All patients managed with tap, and intravitreal antimicrobials alone also demonstrated improvement in visual acuity. Although initial management by vitrectomy was often individualized, a greater proportion

Endogenous *Candida* endophthalmitis diagnosis is based on the combination of clinical setting and typical fundal lesions. There is a well-known association between systemic and ocular *Candida* infections and IVDU. In the mid-1980s, an outbreak of candidiasis after the introduction of a new "brown heroin" onto the drug market occurred in Paris.¹⁰ It has also been shown that 8% of patients enrolled in drug rehabilitation and substitution programs continue to use the intravenous route.¹¹ Hirsbein et al¹² reported on the incidence of endogenous *Candida* endophthalmitis in drug misusers injecting the heroin substitute buprenorphine. Over 9 years, 7 patients were treated with EFB secondary to intravenous use of buprenorphine. All patients underwent posterior vitrectomy, and they had a culture positivity rate of 71.4% (all *Candida* species) with poor visual outcome in 3. In our group, five patients were on buprenorphine treatment, with similar final visual acuities and two patients undergoing vitrectomy. Furthermore, Martinez-Vazquez et al¹³ reported on 15 patients with *Candida albicans* endogenous endophthalmitis; a culture positivity rate of 46% and an early vitrectomy rate of 46.7% were observed, with favorable visual outcomes. Chakrabarti et al, in 2008, reported on 14-year experience of fungal endophthalmitis. They reported on 113 patients with fungal endophthalmitis during this period, of which 12 were endogenous in etiology. The risk factors isolated among their EFB group included uncontrolled diabetes (n = 5), intravenous antibiotic use (n = 4), a contaminated infusion (n = 1), and intravenous drug abuse (n = 2).¹⁴ By comparison, over a 7-year period, of 27 patients of EFB presenting to our unit, 19 were found to be secondary to IVDU.

In the present study, we describe the largest series to date of microbiologically proven IVDU-associated EFB from a single center. Our culture positivity rate was 68.4% overall, with all positive cultures isolating *Candida* species (Table 1). Initial isolation rates with needle aspiration and formal vitrectomy were 66.7 and

of those managed with vitrectomy presented with a poor fundal view in comparison to those managed with tap and injection alone. Tap and injection in our series was curative in 9 of 12 patients, with the remaining 3 requiring vitrectomy for lack of resolution or worsening of disease. No patients underwent enucleation. Furthermore, the association between buprenorphine and IVDU prompted a public health campaign with a subsequent lowering in incident cases (data not shown).

Visual acuity results tended to be favorable irrespective of the method of management in our series. Those patients managed with tap and injection improved over the duration of the study. In our series, 100% of patients achieved a final visual acuity greater than or equal to counting fingers, with 50% achieving $\geq 6/18$ visual acuity. Previous studies have reported on the benefit of vitrectomy in management.^{1,2,20-22} Indeed, Shen and Xu demonstrated a postsurgical visual acuity greater than or equal to counting fingers in 63% of patients managed with vitrectomy. In our series, of those treated with vitrectomy, 90% achieved a postvitrectomy final visual acuity greater than or equal to counting fingers (despite 3 patients losing 1 line of visual acuity), with over 60% gaining ≥ 2 lines of visual acuity and 60% achieving $\geq 6/18$ visual acuity. The management via vitrectomy or otherwise is difficult to elucidate in this complex condition. Indeed, few published guidelines exist on clinical criteria that would commit to a definitive management pathway in this condition. The results of the endophthalmitis vitrectomy study are not applicable directly to a disease with a very different pathogenesis.^{23,24} Future studies with increased numbers would be needed to address this problem.

In conclusion, IVDU-associated fungal endophthalmitis is a disease with associated ocular morbidity. A high clinical suspicion with a judicious history is necessary to allow prompt diagnosis and treatment. Visual results, in paradox to bacterial endogenous endophthalmitis, tend to be favorable.

Key words: endophthalmitis, fungal, drug abuse, microbiology, visual.

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