Candida dubliniensis endophthalmitis: five cases over 15 years

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Abstract

Background: Recent studies have shown that the recently identified organism Candida dubliniensis is less pathogenic than the more common Candida albicans. Due to its rare nature, C. dubliniensis has been previously reported as the causative organism in endophthalmitis in only three cases. We undertook a multicenter, retrospective, consecutive case series to describe the clinical features and outcomes of patients with culture-proven C. dubliniensis endophthalmitis. Medical records were reviewed for all patients with C. dubliniensis endophthalmitis on vitreous/aqueous cultures from June 1998 to June 2013 from all public hospitals throughout Queensland, Australia.

Results: Six eyes from five patients were identified - four males and one female aged from 21 to 55 years (mean 37 years). Four patients were intravenous drug users and four patients had hepatitis C. All five patients were treated with systemic antifungal therapy and intravitreal antifungal injections, and all required vitrectomy. Two eyes developed retinal detachment over the course of the endophthalmitis. Five eyes had visual outcomes of 20/60 or better, and one eye had a poor outcome with final visual acuity of hand movements only. There was no associated mortality, and no infected eyes required enucleation or evisceration.

Conclusions: C. dubliniensis endophthalmitis is a rare condition which occurs mainly in intravenous drug users and can occur in both HIV-positive and HIV-negative patients. Unlike C. albicans endophthalmitis, C. dubliniensis endophthalmitis has reasonable visual outcomes and does not appear to be associated with high mortality.

Keywords: Endophthalmitis; Fungal endophthalmitis; Candida; Candida dubliniensis

Background

Endogenous fungal endophthalmitis is a rare, potentially blinding complication of systemic fungal infection. Overall, the commensal yeast Candida albicans is the most common fungal isolate in patients with endogenous fungal endophthalmitis, although other Candida strains have been implicated as causative organisms including Candida tropicalis, Candida parapsilosis, Candida glabrata, Candida guilliermondii, Candida krusei, and more recently Candida dubliniensis [1]. C. dubliniensis was first identified in 1995 in Ireland as an oral commensal isolated from HIV-infected individuals and has since been isolated in a variety of other candidal infections [2]. Although C. dubliniensis was initially identified as an ‘atypical’ form of the more common C. albicans, subsequent phenotypic and genotypic studies have identified it as a separate strain [2]. Further studies have shown that C. dubliniensis and C. albicans differ not only phenotypically but also in terms of epidemiology, virulence characteristics, and the ability of C. dubliniensis to develop fluconazole resistance [3]. Due to these variations, it is important to differentiate these strains in clinical situations like Candida endophthalmitis due to potential differences in presentation, treatment, and clinical outcomes. To our knowledge, there have been only three previously reported cases of endophthalmitis caused by C. dubliniensis since the discovery of the organism [4-6]. We report and discuss the significance of five new cases of C. dubliniensis endophthalmitis identified over 15 years in public hospitals in Queensland, Australia.

Methods

Queensland public hospital pathology records were reviewed for all patients with endophthalmitis and vitreous/aqueous samples that cultured C. dubliniensis.
over a 15-year period from June 1998 to June 2013. Five patients were identified over this period. The medical records of these patients were then retrospectively reviewed for demographic data, background medical history, presenting signs and symptoms, diagnostic testing, microbiology results, treatment received, visual outcome, and mortality. This review was conducted in accordance with guidelines set forth by the Declaration of Helsinki and was exempt from institutional review board approval.

Results

Age, sex, and predisposing factors

Six eyes from four males and one female aged from 21 to 55 years (mean 37 years) were identified for our series (Tables 1 and 2). All patients had endogenous endophthalmitis, but only two patients had other symptoms of systemic illness with the other three patients having isolated endophthalmitis only. Four patients had a background of intravenous drug use (80%), four patients had hepatitis C (80%), one patient had associated liver cirrhosis (20%), and one patient had associated Candida endocarditis (20%). The four patients with hepatitis C were not being treated with antiviral therapy at the time of presentation. Two patients had intravenous lines in situ at the time of presentation (40%). All five patients had no previous ophthalmic history, and all had best-corrected visual acuities of better than 20/32 in both eyes before presentation for endophthalmitis.

Presentation and diagnosis

In terms of referral pathway, three patients presented to the hospital ophthalmology outpatient department with a mean time from onset of symptoms to ophthalmologic review of 6.3 days. Two patients were current hospital inpatients, and the mean time from onset of symptoms to ophthalmologic review in these patients was 1 day. The right eye was affected in three cases and the left eye in one case, and there was one case of bilateral endophthalmitis. Visual acuity was 20/200 or worse in the affected eye in all patients at presentation (Table 1). The major presenting symptom in all cases was decreased visual acuity. On examination, all patients had severe anterior chamber inflammation and severe vitritis. No patient presented with hypopyon. Two patients had evidence of vitreous snowballs.

Diagnostic testing and microbiology

Systemically, all patients had blood cultures, HIV serology, and echocardiography on presentation. A total of 19 blood cultures were collected from the five patients (mean 3.8 per patient, range 1–8). Only 4 of these 19 cultures were positive for C. dubliniensis (22%), and all 4 of these were collected from the patient with bilateral endophthalmitis. All patients were HIV negative on serology at the time of presentation. Echocardiography showed associated endocarditis in one patient.

In terms of ophthalmic investigations, between the six eyes, five vitreous taps were performed with three samples (60%) producing positive C. dubliniensis cultures. No anterior chamber taps were performed. Seven vitrectomy samples were taken from the six eyes with three intraoperative vitreous samples (43%) producing positive C. dubliniensis cultures. The mean length of time for notification of a positive vitreous C. dubliniensis culture was 5.4 days (range 3–10 days). In terms of antifungal sensitivities, all six isolates were sensitive to fluconazole, 5-flucytosine, and voriconazole; however, only three isolates were sensitive to amphotericin B.

Treatment

In terms of initial treatment, five eyes (83%) from four patients were treated with vitreous tap, intravitreal injection of an antifungal agent, and systemic antifungal therapy on the day of presentation. One eye from one patient was initially treated with urgent vitrectomy, intravitreal injection of an antifungal agent, and systemic antifungal therapy on the day of presentation (17%).

Systemically, the empirical antifungal agent administered was fluconazole in two patients (40%), voriconazole in two patients (40%), and amphotericin B in one patient. Once positive C. dubliniensis culture was obtained, three patients were treated with systemic fluconazole (60%) and two patients were treated with systemic voriconazole (40%). For the patients treated with fluconazole, the mean duration of treatment was 40 days (range 36–42 days). For the patients treated with voriconazole, the mean duration of treatment of 40.5 days (range 35–46 days).

In terms of ophthalmic treatment, all six infected eyes received intravitreal antifungal injections. A total of 33 intravitreal injections were given - 22 voriconazole and 11 amphotericin B. The mean number of intravitreal injections per eye was 5.5 (range 3–10), and the mean interval between intravitreal injections was 4.2 days. All eyes underwent vitrectomy at least once for clearance of infection. The mean time from onset of symptoms to the first vitrectomy was 20.5 days (range 1–43 days). Only one vitrectomy was performed urgently on the day of presentation for diagnosis and for early clearance of infection due to extensive vitreous snowballs. In total, eight vitrectomies were performed on the six eyes - two eyes required two vitrectomies due to subsequent retinal detachments which required repair.

Visual outcomes and mortality

There was no associated mortality in our series, and no infected eye required enucleation or evisceration. No patient developed any secondary fungal infection during follow-up or experienced any systemic complications.
| Case (reference) | Sex, age | Comorbidities | Site | Referral pathway | Initial visual acuity | Antifungal sensitivity | Antifungal treatment and surgery | Final visual acuity |
|------------------|---------|---------------|------|------------------|-----------------------|------------------------|--------------------------------|-------------------|
| Sedeek, 2008 [4] | M, 38   | Nil           | Right eye | Not reported | VA RE - HM, LE - 20/20 | Fluconazole, voriconazole, caspofungin, amphotericin B | Urgent lensectomy/vitrectomy; IVI vancomycin/cefazidime. IVI/topical amphotericin B, PO voriconazole (no duration) | Not reported |
| Pelegrin, 2010 [5] | M, 41  | IVDU, HIV+, hepatitis B and C, fever, neutropenia | Right eye | Presented to eye emergency | VA RE - 20/200, LE - 20/400 | Azoles | Vitrectomy, IVI amphotericin B. Systemic voriconazole then PO fluconazole for 2 months | VA RE - 20/60 |
| Espinosa-Heidmann, 2012 [6] | M, 27 | IVDU, onychomycosis | Left eye | Presented to eye clinic | VA LE - 20/400 | Fluconazole and all other agents tested | Toxoplasma treatment. IV fluconazole. Vitrectomy/IVI amphotericin B. PO fluconazole for 6 weeks | VA LE - 20/80 |
| Present case 1 | M, 50 | IVDU, hepatitis C | Right eye | Walk-in to eye outpatients | VA RE - CF, LE - 20/20 | Fluconazole, 5-flucytosine, voriconazole, amphotericin B | Empirical IVI amphotericin B. Vitrectomy. 2× IVI amphotericin B. PO voriconazole for 46 days | VA RE - 20/30, LE - 20/16 |
| Present case 2 | M, 28 | IVDU | Right eye | Walk-in to eye outpatients | VA RE - 20/200, LE - 20/20 | Fluconazole, 5-flucytosine, voriconazole | Urgent vitrectomy/IVI voriconazole. Empirical systemic voriconazole. 3x IVI amphotericin B. Vitrectomy/buckle/gas. PO fluconazole for 42 days | VA RE - 20/60, LE - 20/20 |
| Present case 3 | M, 34 | IVDU, hepatitis C, endocarditis, PICC | Right eye | Inpatient referral | VA RE - HM, LE - 20/60 | Fluconazole, 5-flucytosine, voriconazole | Empirical fluconazole, IVI amphotericin B. 2x IVI amphotericin B. Vitrectomy. PO voriconazole for 35 days. Vitrectomy/buckle/gas | VA RE - HM, LE - 20/20 |
| Present case 4 | M, 55 | T2DM, hepatitis C, liver cirrhosis, PICC | Bilateral | Inpatient referral | VA RE - 20/200, LE - 20/200 | Fluconazole, 5-flucytosine, voriconazole, amphotericin B | Empirical fluconazole. Right vitrectomy. 10x IVI voriconazole RE. 4x IVI voriconazole LE. Left vitrectomy. PO fluconazole for 42 days | VA RE - 20/60, LE - 20/60 |
| Present case 5 | F, 21 | IVDU, hepatitis C | Left eye | Walk-in to eye outpatients | VA RE - 20/18, LE - 20/200 | Fluconazole, 5-flucytosine, voriconazole, amphotericin B | Empirical voriconazole, IVI amphotericin B. 8x IVI voriconazole. Vitrectomy. PO fluconazole for 36 days | VA RE - 20/16, LE - 20/30 |

**Abbreviations:** CF counting fingers, F female, HM hand movements, IVDU intravenous drug use, IVI intravitreal injection, LE left eye, M male, PICC peripherally inserted central catheter, PO per oral, RE right eye, T2DM type 2 diabetes mellitus, VA visual acuity.
of diagnosis and repair in both cases. The first of these retinal tears. The maculae were still attached on the day of presentation, and subsequent retinal detachment occurred 10 days later. This patient eventually had final best-corrected visual acuity of 20/60. The second patient had an initial vitrectomy 12 days after presentation and developed retinal detachment 2 days later. This patient eventually had final best-corrected visual acuity of hand movements only.

### Table 2 Summary statistics for endogenous C. dubliniensis endophthalmitis

|                         | Queensland series | Previous endogenous cases | Total |
|-------------------------|-------------------|---------------------------|-------|
| Number of patients      | 5                 | 3                         | 8     |
| Number of eyes involved | 6                 | 3                         | 9     |
| Diagnosis and microbiology |                 |                           |       |
| Vitreous taps           | 5                 | 1                         | 6     |
| Positive fungal vitreous taps |   | 1 (100%)                  | 4 (67%)|
| Vitrectomy specimens    | 7                 | 3                         | 10    |
| Positive fungal vitreotomy specimens | | 3 (100%)                  | 6 (60%)|
| Ocular treatment        |                   |                           |       |
| Intravitreal amphotericin (number of eyes) | 3 (50%) | 2 (66%) | 5 (56%) |
| Intravitreal voriconazole (number of eyes) | 4 (66%) | 0 | 4 (44%) |
| Urgent vitrectomy       | 1 (17%)           | 1 (33%)                   | 2 (22%)|
| Total number of vitrectomies | 8 | 3 | 11 |
| Systemic treatment      |                   |                           |       |
| Empirical fluconazole   | 2 (40%)           | 1 (33%)                   | 3 (38%)|
| Empirical voriconazole  | 2 (40%)           | 1 (33%)                   | 3 (38%)|
| Definitive fluconazole therapy | 3 (60%) | 2 (66%) | 5 (56%) |
| Definitive voriconazole therapy | 2 (40%) | 1 (33%) | 3 (33%) |
| Mean duration of antifungal treatment (days) | 40 | 49 | 43 |
| Outcomes                |                   |                           |       |
| Mean duration of follow-up (days) | 345 | 56 | 287 |
| Final best-corrected visual acuity better than 20/80 | 5 (83%) | 2 (100%) | 7 (87%) |
| Final best-corrected visual acuity worse than 20/200 | 1 (17%) | 0 | 1 (13%) |
| Retinal detachment      | 2 (33%)           | 0                         | 2 (22%)|
| Enucleation/evisceration | 0               | 0                         | 0     |
| Mortality               | 0                 | 0                         | 0     |

*Details of final visual acuity have been described only in eight cases.*

In terms of visual outcomes, five eyes (83%) recovered best-corrected visual acuity of 20/60 or better and one eye had a poor final visual acuity of hand movements only. No eyes developed associated cataract or glaucoma. Two eyes did develop retinal detachment over the course of the endophthalmitis which required surgical repair. Both detachments were caused by single superior retinal tears. The maculae were still attached on the day of diagnosis and repair in both cases. The first of these two patients had initially undergone urgent vitrectomy on the day of presentation, and subsequent retinal detachment occurred 10 days later. This patient eventually had final best-corrected visual acuity of 20/60. The second patient had an initial vitrectomy 12 days after presentation and developed retinal detachment 2 days later. This patient eventually had final best-corrected visual acuity of hand movements only.

### Discussion

It is well documented that Candida species are among the most common known fungal pathogens. They can cause a wide range of diseases in humans from superficial mucosal infections to life-threatening disseminated diseases. By far, the most prevalent isolated strain is C. albicans which has been implicated in up to 65% of cases of candidemia [7]. Although C. albicans has been shown to have low virulence in healthy individuals, candidiasis is associated with relatively high rates of morbidity and mortality [8]. Among patients with diagnosed candidemia, reported rates of associated endogenous endophthalmitis range from less than 3% to 44% and mortality rates in these patients have been reported as high as 77% [9]. Candida species reported to cause endophthalmitis include C. albicans, C. tropicalis, C. parapsilosis, C. glabrata, C. guilliermondii, C. krusei, and most recently C. dubliniensis.

C. dubliniensis was first described in 1995 in Dublin, Ireland, among HIV-infected patients with oral candidiasis [2]. It has been found to be only a minor component of the oral flora of humans, and although it primarily causes oral candidiasis in HIV-infected and immunocompromised patients, rare reports of invasive systemic infections in both HIV-positive and HIV-negative patients have been documented [10-12]. This is consistent with large epidemiological studies which report that candidemia caused by C. dubliniensis has only rarely been identified and represents around 2% of yeast-positive blood cultures [7]. The rare isolation of C. dubliniensis has also likely been due to its close phenotypic similarity to C. albicans resulting in often misidentification in laboratory settings. In fact, retrospective studies of Candida isolates in fungal stock collections going back to the 1970s have since found many cases of C. dubliniensis that were mistakenly identified as C. albicans [13-15]. This suggests that C. dubliniensis has probably been present in the community for a much longer period than its recent discovery indicates and could also suggest that many cases of C. dubliniensis endophthalmitis have been wrongly attributed to C. albicans in previous published literature.

Thus, due to its rare nature, only recent identification, and probable previous misidentification, C. dubliniensis has only rarely been reported as the causative organism in endophthalmitis. Although the sample size of our series
is small, surprisingly, our five cases of *C. dubliniensis* endophthalmitis represent the largest single case series published to date with only three other previously reported cases to our knowledge in the literature (Tables 1 and 2) [4-6]. The significance of these now eight total cases is important because recent studies have shown that *C. dubliniensis* is less pathogenic than *C. albicans* and this may have implications for the diagnosis and treatment of endophthalmitis caused by these separate organisms.

Comparing the five cases in our series with the three previous cases (Tables 1 and 2), it is clear that risk factors for endogenous *C. dubliniensis* endophthalmitis include male gender, intravenous drug use, hepatitis, liver disease, placement of an intravenous catheter, and endocarditis. It is also important to note that only one previous patient has been HIV positive [5]. In terms of presentation, often these cases present as isolated endophthalmitis infections without any other systemic evidence of disseminated disease.

Diagnosis in *C. dubliniensis* endophthalmitis can be difficult because the organism has high false-negative rates on fungal cultures of both vitreous samples and blood cultures. However, the sensitivities of these investigations in our series were improved compared to previous *C. albicans* endophthalmitis series [16]. Microbiologically, although fluconazole-resistant isolates of *C. dubliniensis* have been described due to overexpression of genes encoding multidrug transporter proteins [17], all isolates from the reported cases of *C. dubliniensis* endophthalmitis have been susceptible not only to fluconazole but most other conventional antifungal agents (Table 1).

In terms of treatment and outcomes, vitrectomy, repeated intravitreal injection, and systemic antifungal therapy appear to be efficacious in *C. dubliniensis* endophthalmitis with 87% of infected eyes recovering vision of 20/80 or better. Only retinal detachment appears to be associated with poorer visual outcomes, while surprisingly, early vitrectomy, increased number of intravitreal injections, and delayed presentation all appear to not influence visual outcomes.

Most interestingly, the visual outcomes for endogenous *C. dubliniensis* endophthalmitis appear to be slightly better when compared to a recent study into visual outcomes in endogenous *C. albicans* endophthalmitis cases [16]. In this study, 33% of patients with *C. albicans* endophthalmitis had a final visual acuity of 20/200 or worse and 52% of patients had a final visual acuity of 20/40 or worse [16]. These differences in visual outcomes between *C. dubliniensis* endophthalmitis and the more common *C. albicans* endophthalmitis support the hypothesis suggested by Moran et al. that *C. dubliniensis* is less pathogenic than *C. albicans* due to the decreased ability of *C. dubliniensis* to produce hyphae and its intolerance to environmental stressors [18]. This is further supported by the reduced associated systemic mortality in *C. dubliniensis* endophthalmitis.

### Conclusions

Overall, *C. dubliniensis* is a rare cause of both candidemia and endogenous endophthalmitis and can present in both HIV-positive and HIV-negative patients. Based on the albeit limited number of reported endophthalmitis cases caused by this organism, we recommend treatment with intravitreal voriconazole to avoid possible amphotericin B resistance, followed by vitrectomy for clearance of infection and a 6-week course of systemic fluconazole therapy. Although this organism can be resistant to fluconazole, there is no documented case of *C. dubliniensis* endophthalmitis where the isolate has shown this resistance. In addition, although this treatment regime may be complicated by retinal detachment, overall it appears to be associated with improved visual outcomes compared to cases caused by *C. albicans* and does not lead to any associated systemic morbidity or mortality.

### Competing interests

The authors declare that they have no competing interests.

### Authors’ contributions

JP conceived the study and drafted the manuscript. TM identified the patients, reviewed the medical records, conducted the literature review, and drafted the manuscript. Both authors read and approved the final manuscript.

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