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ORIGINAL PAPER

Prevalence of, and risk factors for, hematogenous fungal endophthalmitis in patients with *Candida* bloodstream infection

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Abstract

Purpose Endogenous fungal endophthalmitis (EFE) is a severe consequence of candidemia. The prevalence of, and risk factors for, EFE is not well studied.

Methods We retrospectively collected cases of patients with candidemia who had undergone ophthalmological examination between April 2011 and March 2016 in five regional hospitals. We conducted bivariate and multivariate analyses using patients' age, gender, causative *Candida* species, diabetes status, corticosteroid use, cancer status, neutropenia, intensive care unit admission, presence of central venous catheter (CVC), presence of shock, prior antibiotic use, 30-day mortality, and highest Sequential Organ Failure Assessment (SOFA) score. Data on sustained positive blood culture, β-D glucan, CVC removal, empirical antifungal drug used, and time to appropriate antifungal therapy were also collected if available.

Results Of 174 patients with candidemia, 35 (20.1%) were diagnosed with EFE, including 31 (17.8%) with chorioretinitis and 4 (2.3%) with vitritis. Bivariate analysis (EFE group vs. non-EFE group) found that *Candida albicans* candidemia (77.1 vs. 34.5%, $P<0.001$), neutropenia (14.3 vs. 5.8%, $P=0.141$), CVC placement (94.3 vs. 71.2%, $P=0.004$), and the presence of shock (28.6 vs. 16.5%, $P=0.145$) were each higher in the EFE group. Multivariate logistic regression analysis found *C. albicans* candidemia (adjusted odds ratio 6.48; [95% CI 2.63–15.95]) and CVC placement (7.55 [1.56–36.53]) to be significant risk factors for EFE.

Conclusions *Candida albicans* is the most common causative agent for *Candida* EFE. Patients with candidemia and CVC placement should be closely monitored by ophthalmologists.

Keywords Bloodstream infection · *Candida* · Candidemia · Endophthalmitis

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Purpose

Candida bloodstream infection (candidemia) is a serious systemic infection causing disseminated fungal lesions in multiple organs. The eyes are among the most frequently affected organs. Endogenous fungal endophthalmitis (EFE) is a rare but sight-threatening consequence requiring immediate diagnosis and appropriate treatment [1]. It is recommended that all patients with candidemia undergo funduscopic examination at the time of diagnosis and be closely monitored afterward, because ocular involvement sometimes appears later [2, 3]. EFE is classified as either vitritis (endophthalmitis sensu stricto) or chorioretinitis (infection in the retina and choroid). Fungal vitritis is characterized by recognizable vitreous inflammation, and fungal chorioretinitis is characterized by an infiltrative chorioretinal lesion without evidence of vitreous involvement [4]. Vitritis is more severe and sometimes requires vitrectomy.

The prevalence of EFE in patients with candidemia has been studied. However, the reported prevalence of EFE (chorioretinitis and vitritis) varied from 6.9 to 37% in those previous studies, which were performed mainly from the 1980s to 2000s [2, 5–8]. One study published in 2007 reported only one case in 46 (2.2%) subjects [9]. The prevalences of chorioretinitis and vitritis also have a wide range of reported values (chorioretinitis, 2.1–11%; vitritis, 0–1.6%) [4, 9–11]. Several small studies have suggested that the presence of a central venous catheter (CVC) and immunosuppression are risk factors for developing EFE [4, 12]. The incidence of healthcare-associated candidemia is expected to become increasingly more likely because of advances in medical and surgical technologies [13]. Here, we studied the prevalence of, and risk factors for, EFE in patients with candidemia in the years 2012–2017.

Patients and methods

We conducted a retrospective cohort study of consecutive cases of candidemia collected between April 2012 and March 2017 from the medical records of five regional and university hospitals in Japan. A diagnosis of candidemia was made from at least one positive result for a *Candida* species in blood culture. Of the 289 cases of candidemia collected from the records of adult patients (age ≥ 18 years), we excluded 115 cases that included no ophthalmological examination. The 174 cases (60.2% of the 289 cases of candidemia collected) included in this study were collected from the following centers: Yokohama Municipal Citizen's Hospital (650 beds), 72 cases; Yokohama City University Hospital (672 beds), 37 cases; Yokohama City University Medical Center (726 beds), 36 cases; Fujisawa City Hospital (536 beds), 15 cases; and National Hospital Organization Yokohama Medical Center (500 beds), 14 cases. This study was approved by the ethics committee at each participating institution. (The approval numbers were 201611-03, B160900004, D1401020, F2016032, and 28-19, respectively.)

The predisposing conditions and clinical status at the time of onset of candidemia (i.e., the time when the blood culture sampled positive for *Candida*) were obtained from the medical records using case report forms. This information included gender, age, causative *Candida* species, presence of diabetes, corticosteroid use (use over 1 week, regardless of dosage), presence of cancer, neutropenia (absolute neutrophil count < 500/μL), intensive care unit (ICU) admission, presence of a central venous catheter (CVC), and presence of shock at the time of disease onset. Ophthalmological findings were classified as vitritis or chorioretinitis, as defined by the descriptions of a specialist ophthalmologist [4]. Data on clinical course and the prognosis were also collected; this information included use of antibiotics before onset, 30-day mortality (death within 30 days of onset), and the highest Sequential Organ Failure Assessment (SOFA) score during the observation period. Other clinical and laboratory data were optionally obtained if clearly documented in the medical records; these included sustained fungemia (repeatedly positive for the same *Candida* species in separate blood cultures performed over a period of 48 h or more), serum β-D glucan positivity, CVC removal after diagnosis, empirical antifungal drug used, and time to appropriate antifungal therapy (AAT) after positive blood culture. These optional data were used only for bivariate analysis. Serum β-D glucan titers were measured using commercial laboratory tests (WAKO beta-glucan test, Wako Pure Chemical Industries, Ltd., Osaka, Japan; Fungitec-G/MK, Seikagaku, Kogyo, Tokyo, Japan), and positivity for serum β-D glucan was determined according to the manufacturers' instructions.

Continuous data are presented as means and 95% confidence intervals (CIs) or medians and interquartile ranges (IQRs). Categorical data are presented as numbers and percentages. Data were analyzed using two-tailed Mann–Whitney *U* test for comparisons of continuous variables between two or three groups and by Fisher's exact test or Chi-square test for comparisons of categorical data. Statistical analyses were performed with Mac Toukei-Kaiseki Ver. 2.0 software (Esumi, Tokyo, Japan) and Prism 7 (GraphPad Software, San Diego, CA, USA). *P* values < 0.05 were considered statistically significant.

Results

Prevalence of endogenic fungal endophthalmitis (chorioretinitis and vitritis)

We identified 174 patients with candidemia who had undergone ophthalmological examination. Of these, 35 (20.1%) were diagnosed as having EFE [four (2.3%) with vitritis and 31 (17.8%) with chorioretinitis]. Of the four patients with vitritis, three were diagnosed at first consultation with the ophthalmologist and one was diagnosed 2 weeks after the onset of candidemia, despite the absence of ophthalmologic findings at the first consultation. Although other underlying diseases such as hypertension, diabetes mellitus, concurrent bacteremia, and HIV infection are known to cause mimic lesions on the retina [10], of the seven EFE patients with diabetes mellitus, six were judged by the ophthalmologists to most likely have EFE rather than diabetic retinopathy (the details were unknown in the one remaining case). No cases with concurrent bacteremia were found among patients with EFE, and no intravenous drug users or HIV-positive cases were reported in this study cohort.

Analysis of underlying risk factors for endogenic fungal endophthalmitis

Demographic and clinical characteristics of this study population are shown in Table 1. Median age was 67.5 years and there were 110 men (63.2%). There was no significant difference with respect to the department to which they were admitted (medical, surgical, or emergency department). *Candida albicans* fungemia was found significantly more often in the EFE group than in the non-EFE group (77.1 and 34.5%, $P < 0.001$). With regard to underlying conditions, there was no significant difference between the two groups in terms of diabetes (20.0 and 14.4%), corticosteroid use

Table 1 Characteristics, causative agents, and predisposing conditions of the study subjects

	Total ($N = 174$)	Candidemia with EFE ($N = 35$)	Candidemia without EFE ($N = 139$)	*P* value
Male gender—no. (%)	110 (63.2)	24 (68.6)	86 (61.9)	0.789
Age—years, median [IQR]	67.5 [55–77]	66 [51–76]	68 [56–77]	0.273
Admission—no. (%)				
Medical	73 (42.0)	15 (42.9)	58 (41.7)	0.386
Surgery	86 (49.4)	19 (54.3)	67 (48.2)	
Emergency department	15 (8.6)	1 (2.9)	14 (10.1)	
Causative agent—no. (%)				
C. albicans[a]	75 (43.1)	27 (77.1)	48 (34.5)	< 0.001*,[b]
C. parapsilosis	48 (27.6)	4 (11.4)	44 (31.7)	0.019*
C. glabrata	28 (16.1)	1 (2.9)	27 (19.4)	0.018*
C. tropicalis	8 (4.6)	1 (2.9)	7 (5.0)	1.000
Other *Candida* species	11 (6.3)	2 (5.7)	9 (6.5)	
Unidentified	4 (2.3)	0 (0.0)	4 (2.9)	
Underlying conditions and status—no. (%)				
Diabetes	27 (15.5)	7 (20.0)	20 (14.4)	0.436
Corticosteroid use	24 (13.8)	3 (8.6)	21 (15.1)	0.417
Cancer	54 (31.0)	14 (40.0)	40 (28.8)	0.223
Neutropenia	13 (7.5)	5 (14.3)	8 (5.8)	0.141
ICU admission	55 (31.6)	13 (37.1)	42 (30.2)	0.425
Central venous catheter placement	132 (75.9)	33 (94.3)	99 (71.2)	0.004*
Presence of shock	33 (19.0)	10 (28.6)	23 (16.5)	0.145
Antibiotic use	110 (63.2)	25 (71.4)	85 (61.2)	0.328
30-day mortality	34 (19.5)	8 (22.9)	26 (18.7)	0.634
Highest SOFA score	3 [1–6]	4 [1–6]	3 [1–6]	0.751

EFE endogenic fungal endophthalmitis, *ICU* intensive care unit, *SOFA* sequential organ failure assessment

[a]Including one case of mixed fungemia of *C. albicans* and *C. parapsilosis*

[b]Compared with other *Candida* species

*Statistically significant

(8.6 and 15.1%), cancer (40.0 and 28.8%), ICU admission (37.1 and 30.2%), previous antibiotic use (71.4 and 61.2%), 30-day mortality (22.9 and 18.7%), and highest SOFA score (median and IQR, 4 [1–6] and 3 [1–6]). The CVC placement (94.3 and 71.2%, $P=0.004$) was higher in the EFE group. We conducted a multivariate logistic regression analysis selecting as risk factors *C. albicans* fungemia, the presence of neutropenia, CVC placement, and the presence of shock. *C. albicans* fungemia (adjusted odds ratio, 6.48; 95% CI [2.63, 15.95]) and CVC placement (7.55 [1.56, 36.53]) were found to be significantly associated with EFE (Table 2).

Data on other underlying conditions and on clinical course were obtained in some cases in which information was clearly documented (Table 3). The proportions of sustained fungemia (20.0% in the EFE group and 13.8% in the non-EFE, $P=0.401$, in 160 cases), positive serum β-D glucan (95.7 and 79.5%, $P=0.113$, in 106 cases) and time to AAT within 24 h (50.0 and 35.1%, $P=0.118$, in 168 cases) were non-significantly higher in the EFE group. The proportion of CVC removal (90.9 and 94.7%, $P=0.614$, in 79 cases) was non-significantly lower in the EFE group. The empirical antifungal drug used (in 171 cases) did not differ between the EFE group and non-EFE group.

Table 2 Multivariate logistic regression analysis for the risk of endogenic fungal endophthalmitis

	Adjusted odds ratio	95% confidence interval	*P* value
C. albicans fungemia	6.48	[2.63, 15.95]	<0.001*
Neutropenia	3.51	[0.89, 13.85]	0.073
Central venous catheter placement	7.55	[1.56, 36.53]	0.012*
Presence of shock	1.52	[0.58, 3.96]	0.391

*Statistically significant

Discussion

Our retrospective cohort study described the prevalence of EFE (chorioretinitis and vitritis) in patients with candidemia. Chorioretinitis was found in 17.8% of candidemia patients and vitritis was found in 2.3%. The choroid and retina are more likely than the vitreous body to be affected by disseminated *Candida* infection, and the prevalence of chorioretinitis is reported to be higher than vitritis [4]. However, accurately determining the prevalence of EFE in patients with candidemia is a challenging task. Studies of the pathological anatomy of 133 cases of candidemia or invasive fungal infection found ocular involvement in only 18% of subjects before they died [14]. Prospective studies performed before 2000 reported that 26–37% of patients with candidemia developed EFE [2, 6, 8]. The largest prospective study to date, which included 370 candidemia cases, reported that

Table 3 Other characteristics and clinical courses of the study subjects

	Total	Candidemia with EFE	Candidemia without EFE	*P* value
No. of data collected	*N*=160	*N*=30	*N*=130	
Sustained fungemia—no. (%)	24 (15.0)	6 (20.0)	18 (13.8)	0.401
No. of data collected	*N*=106	*N*=23	*N*=83	
Positive serum β-D glucan	88 (83.0)	22 (95.7)	66 (79.5)	0.113
No. of data collected	*N*=79	*N*=22	*N*=57	
CVC removal—no. (%)	74 (93.7)	20 (90.9)	54 (94.7)	0.614
Empirical antifungal drug used—no. (%)				
No. of data collected	*N*=171	*N*=35	*N*=136	
Micafungin	137 (80.1)	28 (80.0)	109 (80.1)	1.000[a]
Fluconazole	27 (15.8)	6 (17.1)	21 (15.4)	0.798
Liposomal amphotericin-B	5 (2.9)	1 (2.9)	4 (2.9)	
No treatment	2 (1.2)	0 (0.0)	2 (1.5)	
Time to appropriate antifungal therapy—no. (%)				
No. of data collected	*N*=168	*N*=34	*N*=134	
<24 h	64 (38.1)	17 (50.0)	47 (35.1)	0.118[b]
<48 h	50 (29.8)	9 (26.5)	41 (30.6)	0.305
≥48 h	52 (31.0)	8 (23.5)	44 (32.8)	
No treatment	2 (1.2)	0 (0.0)	2 (1.5)	

EFE endogenic fungal endophthalmitis, *CVC* central venous line

[a]Compared with other antifungal agents

[b]Compared with longer time or no antifungal treatment

the prevalence of chorioretinitis was 11% and that of vitritis was 1.6% [11]. Because the incidence of candidemia is reported to be increasing—from 0.2/1000 patient-days in 1995 to 0.4/1000 patient-days in 2000 [15]—the prevalence of EFE is also expected to be increasing. Our results were consistent with these previous findings, and we consider that we have successfully described the increase in cases of EFE, despite ours being a retrospective study. However, reports on EFE patients who were diagnosed by ophthalmologists have suggested that only 17% had signs of systemic infection and 72% were affected by disseminated lesions in other organs [16, 17]. Positive blood culture was observed in only 33% of patients diagnosed by ophthalmologists as having bacteremic or fungemic endophthalmitis [18]. Further investigation will be needed to determine the prevalence of EFE in the patients with candidemia.

Historically reported risk factors for developing systemic blood stream infection include broad-spectrum antibiotic use, gastrointestinal surgery, generalized immunosuppression, intravenous drug abuse, indwelling intravenous catheters, parenteral hyperalimentation, and multiple-organ involvement [7]. Among these, presence of a CVC is a major risk factor for developing candidemia. In this study, CVC placement (94.3%) was notably high in the EFE group. The odds ratio of CVC placement as a risk factor for developing EFE was 7.55 (95% CI [1.56, 36.53]). We consider that CVC placement is responsible not only for candidemia, but also for the development of EFE. Early removal of CVC improves the prognosis of patients with candidemia [19]. Another study has also suggested that early removal of CVC improves the prognosis of candidemia patients, but only in cases of catheter-related candidemia [20]. However, we failed to find a relationship between the prevalence of EFE and CVC removal, possibly because of the small number of cases where removal or retention of the CVC was clearly documented. A previous study suggested that neutropenia and a high score on the Acute Physiology and Chronic Health Evaluation (APACHE II) were also significant factors for a deteriorating prognosis in patients with candidemia [20]. We adopted the SOFA score as a severity score in this study, but we found no correlation between SOFA score and prevalence of EFE. Multivariate analysis failed to reveal any significant relationship between the presence of neutropenia and EFE.

It was expected that a short time to AAT (appropriate antifungal treatment) would be a major factor in improving the prognosis of the patients with candidemia or with *C. glabrata* fungemia [21, 22], and also that delayed or inappropriate antifungal therapy would increase mortality in patients with candidemia [23]. However, inconsistent with that expectation, there was no significant correlation between prevalence of EFE and the time to AAT within 24 h in our study cohort. It is widely known that EFE can become symptomatic and detectable only weeks after the onset of candidemia [1, 11], and we found one patient in our study who was diagnosed with vitritis 2 weeks after the onset of candidemia. With regard to appropriate antifungal therapy, candin agents (for example, micafungin) are not recommended for the treatment of EFE because of their poor penetration into the eye [24]. However, although fluconazole, voriconazole, and liposomal amphotericin-B are recommended for the treatment of EFE [25, 26], micafungin is widely used in Japan for the treatment or prophylaxis of deep-seated *Candida* infections. Because there was no significant correlation between prevalence of EFE and the time to AAT or the choice of antifungal agent, we consider that these factors were not critical matters in the prevention of EFE in patients with candidemia.

Our study had several limitations. Because it was retrospective study, the prevalence of EFE was not accurate due to selection bias. We were not able to obtain details sufficient to differentiate EFE from retinopathy as a complication of diabetes mellitus or hypertension, because the diagnosis of EFE and the follow-up were performed by ophthalmologists in participating hospitals, instead of a set of diagnostic criteria standardized across the study being used. A recent report has suggested that only 50% of patients with candidemia undergo ophthalmological examination [27]. In our cohort, 174 out of 289 patients with candidemia (60.2%) underwent ophthalmologic examination, but in many of them the diagnosis of EFE was based solely on funduscopic findings, not on culture from the eye. Despite its limitations, our study showed the prevalence of, and risk factors for, EFE following *Candida* bloodstream infection in the years 2012–2017 at tertiary medical centers. Patients with *C. albicans* fungemia with CVC placement should be closely monitored by ophthalmologists.

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Compliance with ethical standards

Ethical standards This study was approved by the ethics committee at each participating institution.

Conflict of interest Hideaki Kato received grants from Shionogi and Company, Limited. Other co-authors have no conflict of interest to declare.

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