Risk factors and outcomes of patients with ocular involvement of candidemia

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Abstract

Background
Ocular involvement of candidemia can result in serious complications, including vision loss. This study investigated the risk factors for ocular involvement in patients with candidemia and the outcomes of treatment.

Methods
Episodes of candidemia in hospitalized adults who underwent ophthalmic examinations within 2 weeks of candidemia onset between January 2014 and May 2017 were retrospectively reviewed. Their demographic characteristics, antifungal treatments, and visual outcomes were evaluated.

Results
During the study period, 438 adults were diagnosed with candidemia, with 275 (62.8%) undergoing ophthalmic examinations within 2 weeks of candidemia onset between January 2014 and May 2017 were retrospectively reviewed. Their demographic characteristics, antifungal treatments, and visual outcomes were evaluated.

Persistent candidemia (adjusted odd ratio [aOR], 2.55; 95% confidence interval [CI], 1.29–5.08; P = 0.01), neutropenia during the preceding 2 weeks (aOR, 2.92; 95% CI, 1.14–7.53; P = 0.03), and C. albicans infection (aOR, 2.15; 95% CI, 1.09–4.24; P = 0.03) were independently associated with ocular involvement. Among the 24 patients with neutropenia, 41.7% had ocular involvements at the initial examination. Ophthalmologic examination even before the neutrophil recovery was positive in one-third of neutropenic patients. Out of the 37 patients in whom ocular outcomes after 6 weeks were available, 35 patients showed favorable or stable fundoscopic findings. Two patients had decreased visual acuity despite the stable fundoscopic finding.
Conclusion

Neutropenia within two weeks of candidemia was a risk factor for ocular involvement. More than 80 percent of patients with ocular involvements were asymptomatic, emphasizing the importance of routine ophthalmic examinations. The median 6 weeks of systemic antifungal treatment resulted in favorable outcomes in 89.2% of patients.

Introduction

Candidemia is a common cause of bloodstream infection worldwide and is frequently associated with significant morbidity and mortality rates [1]. *Candida* can infect nearly every organ in the body and many types of prosthetic materials, with the female genital tract, oral mucosa, kidney, brain, heart, and eyes being the sites most commonly affected [2]. Endophthalmitis is a rare but severe form of ocular inflammation caused by infection of the intraocular cavity, and can lead to irreversible visual loss if not treated properly and promptly [3]. Rates of *Candida* endophthalmitis have been reported to range from 0% to 1.6% [4–7], and rates of total ocular involvement from 2.7% to 37% [4–9]. Fundoscopic examination is important in patients with candidemia, because patients with ocular involvement require prolonged antibiotic therapy, and often necessitate adjuvant therapy such as intravitreal treatment or surgery. Although these patients are usually treated with systemic antifungal agents for 4–6 weeks, few studies to date have assessed treatment outcomes in candidemia patients with ocular involvement [4–9]. This study assessed the frequency of ocular involvement and treatment outcomes in patients with candidemia, as well as risk factors for ocular involvement.

Materials and methods

Setting, patients, and study design

All episodes of candidemia in adult patients hospitalized at Asan Medical Center, a 2,700-bed tertiary referral center in Seoul, South Korea, between January 2014 and May 2017 were retrospectively evaluated, and those patients who underwent ophthalmic examinations within 2 weeks of candidemia onset were selected. Fundoscopic findings were reviewed, and ocular infections were categorized as endophthalmitis or chorioretinitis and further classified as ‘proven’, ‘probable’, or ‘possible’ by a retinal specialist [6, 7].

General definitions

Candidemia was defined as the presence of at least one blood culture positive for *Candida* species. If patients had more than one episode of candidemia, only the first episode was analyzed. Neutropenia was defined as an absolute neutrophil count <500 cells/μL. Any duration of neutropenia within 2 weeks prior to candidemia onset was counted. Corticosteroid therapy was defined as receiving systemic glucocorticosteroids for any reason in the past six weeks, regardless of dose [10]. Persistent candidemia was defined as persistently positive blood cultures ≥72 hours following treatment initiation [11].

Definition of ocular involvement of candidemia

Proven ocular infection was defined as ocular lesions in combination with positive culture of vitreous aspirates. Probable endophthalmitis was defined as vitritis or fluffy lesions with
extension into the vitreous. Probable chorioretinitis was defined as deep focal white infiltrates in the retina. In addition, hemorrhage, Roth spots, and nerve fiber layer infarctions (cotton wool spots) in candidemia patients were classified as probable chorioretinitis if no other cause for these abnormalities (e.g., diabetes mellitus, hypertension, or thrombocytopenia) could be identified. Possible chorioretinitis was defined as signs of chorioretinitis observed in patients with underlying systemic diseases that may cause similar lesions (e.g., diabetic or hypertensive retinopathy, thrombocytopenia, or cancer metastasis) [6, 7].

Statistical analysis
Categorical variables were compared using the \( \chi^2 \) or Fisher’s exact test, as appropriate, and continuous variables were compared using Student’s t-test or the Mann-Whitney U-test, as appropriate. All tests of significance were two-tailed, and \( P \) values <0.05 were considered statistically significant. Risk factors for ocular involvement were analyzed by backward stepwise logistic regression analysis. All variables significant in the univariate analysis and other variables of clinical importance were included in a multiple logistic regression model. All statistical analyses were performed using SPSS for Windows software package, version 24 (SPSS Inc., Chicago, IL, USA).

Ethical approval
This observational study was approved by the institutional review board of the Asan Medical Center (IRB No. 2017–0794). To protect personal privacy, identifying information in the electronic database was encrypted. Informed consent was waived by the ethics committee because no intervention was involved and no patient-identifying information was included.

Results
Comparison of characteristics of patients according to ophthalmic examination
Of the 438 patients diagnosed with candidemia during the study period, 163 (37.2%) did not undergo fundoscopic examination within 2 weeks of candidemia onset. Patients with persistent candidemia were more likely to undergo ophthalmic examinations compared with those without (20.4% versus 8.3%; \( P = 0.002 \)). Compared with patients who underwent ophthalmologic examination, those who did not had higher likelihood of septic shock state (16.0% versus 35.0%; \( P < 0.001 \)), early mortality (2.5% versus 28.8%; \( P < 0.001 \)), and 30-day mortality (17.8% versus 48.8%; \( P < 0.001 \)). (Table 1).

Characteristics of patients with ocular involvements
Of the 438 adult patients diagnosed with candidemia during the study period, 275 (62.8%) underwent ophthalmic examinations within 2 weeks after diagnosis of candidemia. Patients underwent ophthalmic examinations a median 6 days (interquartile range [IQR], 4.0–8.0 days) after candidemia onset. Of the 275 patients who underwent ophthalmic examinations, 59 (21.4%) had ocular involvement, including eight (2.9%) with endophthalmitis and 51 (18.5%) with chorioretinitis. All eight patients with endophthalmitis were classified as having probable disease, because none underwent vitreous sampling (Fig 1). Of the 59 patients with ocular involvement, 47 (79.7%) patients showed involvement in both eyes, nine (15.3%) showed only right eye involvement, and three (5.1%) had only left eye involvement. Of these 59 patients, nine (15.3%) could not describe their subjective visual symptoms due to severe illness or weakened mental state, whereas 11 (18.6%) reported visual disturbances, including four of eight
Table 1. Demographic factors, clinical manifestations, and outcomes in patients according to ophthalmic examination within 2 weeks of candidemia.

| Characteristic or outcome | Patients who underwent ophthalmic exam (n = 275) | Patients who did not undergo ophthalmic exam (n = 163) | P      |
|--------------------------|-------------------------------------------------|-------------------------------------------------|--------|
| Demographics             |                                                 |                                                 |        |
| Male sex                 | 179 (65.1)                                      | 87 (53.4)                                       | 0.02   |
| Age (mean±SD) (years)    | 63.2±13.8                                       | 61.2±13.9                                       | 0.91   |
| Comorbid conditions      |                                                 |                                                 |        |
| Malignancy               |                                                 |                                                 |        |
| solid organ              | 138 (50.2)                                      | 83 (51.2)                                       | 0.83   |
| hematologic              | 32 (11.7)                                       | 28 (17.2)                                       | 0.11   |
| Diabetes mellitus        | 75 (27.3)                                       | 51 (31.3)                                       | 0.37   |
| Heart failure            | 33 (12.0)                                       | 17 (10.4)                                       | 0.62   |
| Chronic renal disease    | 29 (10.5)                                       | 15 (9.3)                                        | 0.67   |
| Liver cirrhosis          | 21 (7.6)                                        | 21 (12.9)                                       | 0.07   |
| Chronic lung disease     | 14 (5.1)                                        | 6 (3.7)                                         | 0.49   |
| Risk factors (within 6 weeks) |                                               |                                                 |        |
| Prior antibacterial therapy | 261 (94.9)                                     | 156 (95.7)                                     | 0.71   |
| Corticosteroid therapy  | 92 (33.5)                                       | 75 (46.0)                                       | 0.01   |
| Prior surgery            | 88 (32.0)                                       | 51 (31.3)                                       | 0.88   |
| Chemotherapy             | 75 (27.3)                                       | 55 (33.7)                                       | 0.15   |
| Biliary intervention     | 36 (13.1)                                       | 22 (13.5)                                       | 0.90   |
| Neutropenia *            | 24 (8.7)                                        | 17 (10.4)                                       | 0.67   |
| [median, IQR] (days) b   | [8, 5–12]                                       | [9, 5–18]                                       |        |
| Radiosurgery             | 6 (2.2)                                         | 2 (1.2)                                         | 0.72   |
| Clinical characteristics (at onset) |                                               |                                                 |        |
| Fever c                  | 196 (71.3)                                      | 110 (67.5)                                      | 0.40   |
| ICU admission            | 70 (25.5)                                       | 67 (41.1)                                       | 0.001  |
| Septic shock             | 44 (16.0)                                       | 57 (35.0)                                       | <0.001 |
| Portal of entry          |                                                 |                                                 |        |
| Catheter-related         | 144 (52.4)                                      | 69 (42.3)                                       | 0.09   |
| Intra-abdomen            | 65 (23.6)                                       | 57 (35.2)                                       | 0.01   |
| Primary                  | 39 (14.2)                                       | 29 (17.8)                                       | 0.32   |
| Urinary tract infection  | 22 (8.0)                                        | 8 (4.9)                                         | 0.21   |
| Candida species (no. of isolates) |                                               |                                                 |        |
| C. albicans              | 116 (42.2)                                      | 54 (33.1)                                       | 0.06   |
| C. glabrata              | 74 (26.9)                                       | 57 (35.0)                                       | 0.08   |
| C. tropicalis            | 47 (17.1)                                       | 28 (17.2)                                       | 0.98   |
| C. parapsilosis          | 33 (12.0)                                       | 14 (8.6)                                        | 0.27   |
| C. krusei                | 8 (2.9)                                         | 6 (3.7)                                         | 0.66   |
| Other Candida species    | 6 (2.2)                                         | 10 (6.2)                                        | 0.03   |
| Outcomes                 |                                                 |                                                 |        |
| Persistent candidemia    | 56 (20.4)                                       | 14 (8.3)                                        | 0.002  |
| [median, IQR] (days) b   | [8, 6–10]                                       | [9, 7–11]                                       |        |
| Early mortality (7 days) | 7 (2.5)                                         | 47 (28.8)                                       | <0.001 |
| Death within 30 days     | 49 (17.8)                                       | 79 (48.8)                                       | <0.001 |

Data are reported as n (%), except where otherwise indicated.

Abbreviations: SD, standard deviation; HIV, human immunodeficiency virus; IQR, interquartile range; ICU, intensive care unit.

* Within 2 weeks prior to candidemia onset

b The median and interquartile range values were calculated with only the relevant cases.

c Body temperature of the tympanic membrane or axilla at 37.8 °C or higher

https://doi.org/10.1371/journal.pone.0222356.t001
Among 11 patients, 9 patients complained of blurred vision, 1 patient had eye floaters and another developed eye ball pain. Although fundoscopic exam was usually performed only once, two patients with initial negative results were later confirmed to have ocular involvements: one had newly developed blurred vision and the other had repeated ophthalmologic examination due to persistent candidemia.

### Risk factors for ocular involvement

Table 2 compares the characteristics of patients with and without ocular involvement. Corticosteroid use during the preceding 6 weeks (45.8% versus 30.1%; \( P = 0.02 \)), chemotherapy during the preceding 6 weeks (39.0% versus 24.1%; \( P = 0.02 \)), neutropenia during the preceding 2 weeks (16.9% versus 6.5%; \( P = 0.02 \)), \textit{C. albicans} infection (61.0% versus 37.0%; \( P = 0.001 \)), and persistent candidemia (33.9% versus 16.7%; \( P = 0.004 \)) were significantly more frequent among patients with than without ocular involvement. By contrast, \textit{C. glabrata} infection (8.5% versus 31.9%; \( P < 0.000 \)) was significantly less frequent among patients with than without ocular involvement. However, underlying diseases, presumed sources of candidemia, types of antifungal treatment before ophthalmologic examination and clinical characteristics at candidemia onset did not differ significantly in these two groups (Table 2). Multivariate analysis of
Table 2. Demographic characteristics, clinical manifestations, and outcomes in candidemia patients with and without ocular involvement.

| Characteristics or outcome | Patients with ocular involvement (n = 59) | Patients without ocular involvement (n = 216) | P  |
|---------------------------|------------------------------------------|-----------------------------------------------|----|
| Demographics              |                                          |                                               |    |
| Male sex                  | 36 (61.0)                                | 143 (66.2)                                   | 0.46|
| Age (mean±SD) (years)     | 61.0±13.7                                | 63.7±13.9                                    | 0.19|
| Comorbid conditions       |                                          |                                               |    |
| Malignancy                |                                          |                                               |    |
| solid organ               | 28 (47.5)                                | 110 (50.9)                                   | 0.64|
| hematologic               | 8 (13.6)                                 | 24 (11.2)                                    | 0.61|
| Diabetes mellitus         | 12 (20.3)                                | 63 (29.2)                                    | 0.18|
| Chronic renal disease     | 8 (13.6)                                 | 21 (9.7)                                     | 0.40|
| Heart failure             | 5 (8.5)                                  | 28 (13.0)                                    | 0.35|
| Liver cirrhosis           | 3 (5.1)                                  | 18 (8.3)                                     | 0.58|
| Chronic lung disease      | 3 (5.1)                                  | 11 (5.1)                                     | 1.00|
| HIV infection             | 0 (0.0)                                  | 1 (0.5)                                      | 1.00|
| Risk factors (within 6 weeks) |                                      |                                               |    |
| Prior antibacterial therapy | 53 (89.8)                             | 208 (96.3)                                   | 0.05|
| Corticosteroid therapy    | 27 (45.8)                                | 65 (30.1)                                    | 0.02|
| Chemotherapy              | 23 (39.0)                                | 52 (24.1)                                    | 0.02|
| Prior surgery             | 18 (30.5)                                | 70 (32.4)                                    | 0.78|
| Neutropenia               | 10 (16.9)                                | 14 (6.5)                                     | 0.02|
| [median, IQR] (days) b    | [8, 5–11]                                | [8, 5–13]                                    |    |
| Immunosuppressive therapy | 7 (11.9)                                 | 16 (7.4)                                     | 0.27|
| Biliary intervention      | 6 (10.2)                                 | 30 (13.9)                                    | 0.45|
| Radiosurgery              | 2 (3.4)                                  | 4 (1.9)                                      | 0.61|
| Clinical characteristics (at onset) |                                |                                               |    |
| Fever                     | 45 (76.3)                                | 151 (69.9)                                   | 0.34|
| ICU requirement           | 10 (16.9)                                | 60 (27.9)                                    | 0.09|
| Septic shock              | 8 (13.6)                                 | 36 (16.7)                                    | 0.56|
| Portal of entry           |                                          |                                               |    |
| Catheter related          | 30 (50.8)                                | 114 (52.8)                                   | 0.79|
| Intra-abdominal           | 16 (27.1)                                | 49 (22.7)                                    | 0.48|
| Primary                   | 8 (13.6)                                 | 31 (14.4)                                    | 0.88|
| Urinary tract infection   | 3 (5.1)                                  | 19 (8.8)                                     | 0.43|
| Candida species (no. of isolates) |                                |                                               |    |
| C. albicans               | 36 (61.0)                                | 80 (37.0)                                    | 0.001|
| C. tropicalis             | 13 (22.0)                                | 34 (15.7)                                    | 0.26|
| C. glabrata               | 5 (8.5)                                  | 69 (31.9)                                    | 0.000|
| C. parapsilosis           | 3 (5.1)                                  | 30 (13.9)                                    | 0.07|
| C. krusei                 | 2 (3.4)                                  | 6 (2.8)                                      | 0.68|
| Other Candida species     | 1 (1.7)                                  | 5 (2.3)                                      | 1.00|
| Antifungal treatment d    |                                          |                                               |    |
| Fluconazole               | 42 (71.2)                                | 126 (58.3)                                   | 0.10|
| Echinocandin              | 13 (22.0)                                | 77 (35.6)                                    | 0.07|
| Amphotericin              | 4 (6.8)                                  | 11 (5.1)                                     | 0.54|
| Voriconazole              | 0 (0.0)                                  | 2 (0.9)                                      | 0.99|
| Outcomes                  |                                          |                                               |    |
| Persistent candidemia     | 20 (33.9)                                | 36 (16.7)                                    | 0.004|
| [median, IQR] (days) b    | [8, 4–13]                                | [7, 6–9]                                     |    |

(Continued)
factors with \( P \) values <0.05 on univariate analysis found that neutropenia during the preceding 2 weeks (adjusted odds ratio [aOR], 2.92; 95% confidence interval [CI], 1.14–7.53; \( P = 0.03 \)), \( C. \) albicans infection (aOR, 2.15; 95% CI, 1.09–4.24; \( P = 0.03 \)), and persistent candidemia (aOR, 2.55; 95% CI, 1.29–5.08; \( P = 0.01 \)) were independently associated with ocular involvement, whereas \( C. \) glabrata infection (aOR, 0.32; 95% CI, 0.11–0.91; \( P = 0.03 \)) was significantly but inversely associated with ocular involvement (Table 3).

Regarding 24 patients with neutropenia within 2 weeks, 12 patients were neutropenic and the other 12 recovered from neutropenia at the time of candidemia. Four among the 12 neutropenic patients at the time of candidemia showed ocular involvement at initial examination; two of these patients developed more prominent ocular lesions as neutrophil count increased, and two died before neutrophil recovery. Of the eight neutropenic patients with normal fundoscopic results at first examination, only two underwent an additional ophthalmologic examination without any abnormal lesions. Three patients did not undergo subsequent ophthalmologic examination and the other three died before neutrophil recovery. Among the other 12 patients who recovered from neutropenia at the time of candidemia, 6 had ocular involvements at the initial examination. No further ophthalmologic examination was performed for these patients.

### Treatment outcomes of ocular infection

Fundoscopic results 6 weeks after treatment were available for 37 (62.7%) of the 59 patients with ocular involvement. Of the other 22 patients, 17 died before outcomes were assessed and five did not undergo follow-up examinations. The 37 patients included eight with probable

Table 3. Univariate and multivariate analyses of risk factors for ocular infections among patients with candidemia (n = 275).

| Variable               | Univariate analysis OR (95% CI) | Multivariate analysis aOR (95% CI) | \( P \) |
|------------------------|---------------------------------|-----------------------------------|--------|
| Chemotherapy           | 2.02 (1.10–3.71)                |                                   |        |
| Corticosteroid therapy | 1.96 (1.09–3.53)                |                                   |        |
| Neutropenia            | 2.95 (1.23–7.03)                | 2.92 (1.14–7.53)                  | 0.03   |
| \( C. \) albicans      | 2.66 (1.47–4.81)                | 2.15 (1.09–4.24)                  | 0.03   |
| \( C. \) glabrata      | 0.20 (0.08–0.52)                | 0.32 (0.11–0.91)                  | 0.03   |
| Persistent candidemia  | 2.56 (1.34–4.90)                | 2.55 (1.29–5.08)                  | 0.01   |

Abbreviations: aOR, adjusted odds ratio; OR, odds ratio; CI, confidence interval.
endophthalmitis, 23 with probable chorioretinitis, and six with possible chorioretinitis. The causative organisms were *C. albicans* in 22 patients, *C. tropicalis* in eight, *C. parapsilosis* in three, *C. glabrata* in three, and *C. guilliermondii* in one. Of these 37 patients, 34 (91.9%) were treated with fluconazole, and 10 (2.7%) received intravitreal treatment. Follow-up examinations at 6 weeks revealed improved lesions in 29 (78.5%) of the 37 patients, including all eight (100%) with probable endophthalmitis, 17 (73.9%) of 22 with probable endophthalmitis, and four (66.7%) of six with possible chorioretinitis. The ocular lesions in four (17.4%) patients with probable chorioretinitis and two (33.3%) with possible chorioretinitis were similar to the lesions of initial fundoscopic examinations. Ocular lesions worsened in two patients, resulting in vitrectomy (Table 4). Unfortunately, visual acuity results were available only in seven patients, four with endophthalmitis and three with chorioretinitis. Two with endophthalmitis and another two with chorioretinitis did not show full recovery of visual acuity (S1 Table).

**Detailed description of the patients that worsened during treatment**

Two patients had poor ophthalmologic outcomes. One patient was a 32-year-old woman with acute myeloid leukemia who was in a neutropenic state after cytotoxic chemotherapy and was diagnosed with *C. tropicalis* candidemia. She started to receive caspofungin on the day of yeast detection in the blood and fluconazole was added in the following two days. Examination by an ophthalmologist three days after candidemia onset revealed chorioretinitis in both eyes. She received caspofungin alone from the fourth day to the twelfth day after candidemia onset and changed to fluconazole from the thirteenth day. When her eyes were examined three days after the first examination, the chorioretinitis in her right eye had improved but the chorioretinitis in her left eye had been exacerbated during the echinocandin treatment and more aggravated with neutrophil recovery despite systemic fluconazole and intravitreal voriconazole injection. Vitreal hemorrhage occurred, and although the patient underwent vitrectomy, vision was not recovered.

The other patient was a 35-year-old man with Crohn’s disease who required long-term parenteral feeding and was diagnosed with central venous catheter-related *C. albicans* candidemia. He started to receive fluconazole upon detection of yeast in the blood culture and continued to receive fluconazole thereafter. Examination by an ophthalmologist four days after candidemia onset showed chorioretinitis in both eyes. The chorioretinitis in his right eye had improved, but the subfoveal infiltration in his left eye had aggravated during treatment with systemic fluconazole and intravitreal voriconazole injection. He finally underwent vitrectomy of the left eye due to the new epiretinal membrane.

**Discussion**

To our knowledge, few studies have analyzed risk factors and treatment outcomes of ocular involvement in patients with candidemia [4–9]. Of the 275 patients with candidemia who underwent fundus examination during the study period, 59 (21.5%) had fundoscopic abnormalities suggesting ocular involvement of *Candida*. Fungemia with *C. albicans*, persistent candidemia, and neutropenia during the preceding 2 weeks were factors independently associated with ocular involvement, whereas *C. glabrata* was inversely associated with ocular manifestations. Outcomes after 6 weeks of treatment were available for 37 patients, including 34 treated with fluconazole for a median 42 days (IQR, 27–56 days) and 10 who required intravitreal treatment. Fundoscopic findings improved or stabilized after 6 weeks in all but two patients, both of whom underwent vitrectomy. Two patients had decreased visual acuity despite the stable fundoscopic finding. Collectively speaking, we found that 6 weeks of systemic antifungal treatment contributed to good outcomes in 89.2% of patients.
| Age/Sex | Candida Species | Anti-fungal Agent | Intravitreal Injection | Vitrectomy | Treatment Duration | Follow-up fundoscopic findings |
|---------|----------------|-------------------|------------------------|------------|-------------------|-------------------------------|
| 68/M C. tropicalis | Fluconazole | Yes | No | 56 Days | Improved |
| 62/M C. albicans | Fluconazole | Yes | No | 55 Days | Improved |
| 73/F C. tropicalis | Fluconazole | Yes | No | 61 Days | Improved |
| 65/M C. albicans | Fluconazole | Yes | No | 48 Days | Improved |
| 37/M C. tropicalis | Fluconazole, + Amphotericin B | Yes | No | 70 Days | Improved |
| 49/M C. parapsilosis | Fluconazole | No | No | 28 Days | Resolved |
| 38/F C. albicans | Fluconazole | Yes | No | 60 Days | Improved |
| 59/M C. albicans | Fluconazole | No | No | 30 Days | Improved |
| 63/M C. tropicalis | Fluconazole | No | No | 42 Days | Resolved |
| 91/F C. albicans | Fluconazole | No | No | 20 Days | Improved |
| 91/M C. albicans | Fluconazole | No | No | 56 Days | Improved |
| 66/M C. tropicalis | Fluconazole | No | No | 58 Days | Improved |
| 62/M C. albicans | Fluconazole, + Caspofungin | Yes | No | 73 Days | Improved |
| 79/F C. albicans | Fluconazole | No | No | 50 Days | Improved |
| 77/M C. albicans | Fluconazole | No | No | 18 Days | Improved |
| 35/M C. albicans | Fluconazole | Yes | Yes | 89 Days | Aggravated |
| 62/M C. albicans | Fluconazole | No | No | 40 Days | Resolved |
| 74/F C. albicans | Fluconazole | No | No | 24 Days | Resolved |
| 71/M C. albicans | Fluconazole | No | No | 39 Days | Stable |
| 77/M C. albicans | Fluconazole | No | No | 52 Days | Improved |
| 70/M C. albicans | Fluconazole | No | No | 18 Days | Stable |
| 75/F C. tropicalis | Fluconazole | No | No | 25 Days | Improved |
| 32/F C. tropicalis | Fluconazole | Yes | Yes | 97 Days | Aggravated |
| 55/M C. parapsilosis | Amphotericin B | No | No | 28 Days | Improved |
| 61/F C. albicans | Fluconazole | No | No | 42 Days | Resolved |
| 57/M C. parapsilosis | Fluconazole | No | No | 27 Days | Improved |
| 33/M C. albicans | Fluconazole | No | No | 42 Days | Improved |
| 45/F C. albicans | Fluconazole | No | No | 60 Days | Improved |
| 62/F C. albicans | Fluconazole | No | No | 42 Days | Improved |
| 77/M C. albicans | Fluconazole | No | No | 28 Days | Stable |
| 39/F C. albicans | Fluconazole | No | No | 28 Days | Stable |
| 81/M C. tropicalis | Anidulofungin | No | No | 21 Days | Died |
| 68/F C. albicans | Fluconazole | No | No | 25 Days | Died |
| 64/F C. krusei | Amphotericin B | No | No | 34 Days | Died |
| 55/M C. albicans | Fluconazole | No | No | 9 Days | No follow-up |
| 46/F C. albicans | Fluconazole | No | No | 15 Days | Died |
| 43/F C. albicans | Fluconazole | Yes | No | 40 Days | No follow-up |
| 70/M C. albicans | Fluconazole | No | No | 19 Days | Died |
| 53/F C. tropicalis | Micafungin | No | No | 7 Days | No follow-up |
| 76/M C. albicans | Fluconazole | No | No | 13 Days | No follow-up |
| 51/M C. albicans | Fluconazole | No | No | 8 Days | Died |
| 61/M C. albicans | Fluconazole | No | No | 10 Days | Died |
| 65/M C. tropicalis | Anidulofungin | No | No | 15 Days | Died |
| 49/F C. albicans | Fluconazole | No | No | 7 Days | Died |
| 61/F C. albicans | Amphotericin B | No | No | 27 Days | Died |

(Continued)
The rates of ocular involvement of candidemia have been reported to vary, from 0% to 1.6% for endophthalmitis and 2.7% to 37.0% for any ocular involvement [4–9]. In the present study, 59 of 275 (21.5%) patients had fundoscopic abnormalities suggestive of Candida eye involvement. These 59 patients included eight with probable endophthalmitis, 38 with probable chorioretinitis, and 13 with possible chorioretinitis. However, this prevalence may have been underestimated due to selection bias. Of the 438 patients diagnosed with candidemia during the study period, 163 (37.2%) did not undergo fundoscopic examination within 2 weeks of candidemia onset. These patients were significantly more likely to have septic shock and to have a significantly higher mortality rate. Thus this study does not properly reflect the prevalence of ocular involvement of candidemia in patients with more severe disease, who also have many risk factors for ocular involvement.

Our findings support the notion that ocular candidiasis is often asymptomatic [7]. Of the 59 patients with ocular involvement, nine could not describe their subjective visual symptoms due to severe illness or weakened mental state. Only eleven (18.6%) reported visual disturbances, including four of eight (50%) with endophthalmitis and 7 of 51 (13.7%) with chorioretinitis. Blurred vision was the most common symptom, followed by eye pain and eye floaters. Forty (67.8%) had no ocular symptoms in the beginning, and one developed blurred vision during treatment. Candidemia seeds the highly vascular choroid first, so the initial manifestation is usually chorioretinitis or choroiditis [12]. Initially, there may be minimal or no vitreous inflammation. Infection of the choroid and retina often does not cause pain; therefore, unless the lesions are near the macula, patients with early Candida chorioretinitis may be asymptomatic. As the infection worsens, vitritis develops and vision becomes impaired [12]. Therefore, routine fundoscopy to detect ocular candidiasis is recommended, even in patients with candidemia who do not present with visual symptoms. In our study, patients with endophthalmitis were likely to be symptomatic than those with chorioretinitis. However, half of the patients with endophthalmitis did not complain of any visual problems, emphasizing the importance of routine ocular examination.

Risk factors for endogenous Candida chorioretinitis and endophthalmitis are poorly understood, although studies suggest that these risk factors are similar to those for candidemia itself [13, 14]. Fungemia with C. albicans (versus non-albicans species), persistent candidemia,
visual symptoms, immunosuppression, and central catheter placement have been associated with ocular candidiasis [5, 7, 15]. The present study found that fungemia with C. albicans, persistent candidemia, and neutropenia during the preceding 2 weeks were independently associated with ocular involvement. Similar to previous studies, we found that C. albicans was the most common cause of ocular candidiasis, followed by C. tropicalis [7, 16], with C. glabrata infection being significantly less frequent in patients with than without ocular manifestations.

In general, fundoscopic examinations are less sensitive in neutropenic than in non-neutropenic patients [17]. In the present study, we found that four patients, representing one-third of neutropenic patients at the time of candidemia, had ocular involvements. Among them, two patients developed more prominent lesions with neutrophil recovery. Within our limited data, no patients without initial ocular involvements revealed newly developing ocular lesions with neutrophil recovery. Current guidelines recommend performing ophthalmologic examination after neutrophil recovery and echinocandins as initial antifungal therapy for candidemia [17]. Although fundoscopy at the time of neutropenia is relatively insensitive, our data suggests routine ophthalmic examination at the time of neutropenia could also be helpful. Further research is required for optimal timing of sequential fundoscopic examinations and to empirically evaluate antifungal agents administered to patients at high risk for ocular involvement.

Although echinocandin is currently recommended as the first-line antifungal agent for candidemia, there is a growing concern that the use of echinocandin as an initial antifungal therapy may increase the risk of ocular invasion compared with triazoles. The penetration of echinocandins into the eye has been shown to be poor in previous studies [18–20]. However, in the present study, initial echinocandin therapy was not associated with the rate of ocular involvement. Although it can be assumed that echinocandins may reduce the duration of candidemia and counterbalance its negative pharmacologic effect, this assumption could not be verified with our data. Considering that existing data on the rate and outcome of ocular candidiasis in patients initially treated with echinocandins are scarce and conflicting [20–22], further studies need to be carried out to directly address this issue.

Fundoscopic findings improved or stabilized within 6 weeks in 35 of the 37 patients for whom 6 week outcomes were available. Thirty-two patients with favorable fundoscopic outcomes were treated with fluconazole for a median 42 days (IQR, 27–56 days). However, despite favorable fundoscopic outcome, two with endophthalmitis and another two with chorioretinitis did not show full recovery of visual acuity. This shows that 10.8% of patients have vision deterioration. Active treatment strategy including intravenous and intravitreal therapy should be considered because visual acuity reflects the functional outcomes of the eye.

It is recommended that patients with Candida endophthalmitis be treated for at least 4–6 weeks, with the final duration depending on resolution of the lesions [17]. The patients in the present study were treated for a median 6 weeks, with 89.2% experiencing successful outcomes. A total of 18 out of 37 patients (40.5%) were treated for less than 6 weeks (median, 26.5 days; IQR, 19.5–28.5 days). All of them showed favorable fundoscopic outcome in 6 weeks after candidemia onset. We suggest that treatment duration can be optimized to 4 to 6 weeks depending on the severity of ocular invasion. These results are in agreement with clinical practice guidelines.

This study had several limitations. First, it was a single-centered retrospective study in South Korea; multicenter prospective studies are needed to confirm our findings. Second, patients with critical illness without bacteremia or candidemia may have retinal lesions similar to those described here as chorioretinitis [23]. However, differentiating between infectious chorioretinitis and retinal lesions of noninfectious causes is difficult. Thus there could be diagnostic uncertainty of possible cases. However, considering that fundoscopic findings were improved in two-thirds of possible chorioretinitis patients after anti-fungal treatment, we
believe that most of the possible cases truly originated from candidemia and thus do not significantly weaken our findings. Third, although patients may develop new ocular lesions after the start of antifungal treatment [11], periodic follow-up ophthalmic examinations were not performed in patients without baseline abnormalities unless they complained of vision symptoms. Thus, patients with late onset ocular candidiasis may have been omitted.

In conclusion, ocular involvement is common in patients with candidemia and is associated with persistent candidemia, fungemia with *C. albicans*, and neutropenia during the 2 weeks prior to candidemia. Ophthalmologic examination even before neutrophil recovery was positive in one-third of neutropenic patients. More than 80 percent of patients with ocular involvements were asymptomatic, emphasizing the importance of routine ophthalmic examinations. A median 6 weeks of systemic antifungal treatment resulted in favorable outcome in 89.2% of patients, in agreement with current guidelines.

**Supporting information**

S1 Table. Visual acuity results of seven patients with ocular involvement of candidemia. Abbreviations: VA, visual acuity; OD, right eye; OS, left eye. *: Time after the treatment initiation.

(DOCX)

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