CLINICAL STUDY

Should all patients with candidaemia have an ophthalmic examination to rule out ocular candidiasis?

ROHIT KRISHNA, DONALD AMUH, CAREEN Y. LOWDER, STEVEN M. GORDON, KARIM A. ADAL, GERALDINE HALL

Abstract

Purpose **To determine the incidence of ocular candidiasis and length of ophthalmic follow-up required to rule out ocular candidiasis in candidaemic patients.**

Methods **We prospectively studied patients with candidaemia at our institution. Eligibility criteria included a dilated ophthalmological examination within 72 h of fungaemia. Patients without ocular candidiasis on initial examination had follow-up dilated ophthalmoscopy performed at 1, 2, 4, 12 and 24 weeks.**

Results **Between May 1996 and March 1997 a total of 50 patients with fungaemia were identified of whom 31 were included in the study; 15 excluded patients died before an initial examination was performed. The overall incidence of ocular candidiasis was 26% (8/31 patients), all manifested as chorioretinitis. Five patients (16%) had ocular candidiasis on their initial examination. One of 21 patients (5%) without ocular candidiasis on initial examination developed ocular candidiasis within 1 week. Two of 16 patients (13%) without ocular candidiasis on initial examination or at 1 week follow-up developed ocular candidiasis within 2 weeks. No evidence of ocular candidiasis occurred in the 12 patients with follow-up at 4 weeks, the 8 patients with follow-up at 12 weeks and the 4 patients with follow-up at 24 weeks.**

Conclusion **The incidence of ocular candidiasis among hospitalised patients is clinically significant. We recommend ophthalmological follow-up for development of ocular candidiasis for at least 2 weeks after an initial negative eye examination.**

Key words Candida, Candidaemia, Candidiasis, Chorioretinitis, Eye, Fungus

R. Krishna
C.Y. Lowder
Division of Ophthalmology
Cleveland Clinic Foundation
Cleveland, Ohio, USA

D. Amuh
S.M. Gordon
K.A. Adal
Department of Infectious Disease
Cleveland Clinic Foundation
Cleveland, Ohio, USA

G. Hall
Department of Microbiology
Cleveland Clinic Foundation
Cleveland, Ohio, USA

Careen Y. Lowder, MD, PhD ✉
Division of Ophthalmology
Cleveland Clinic Foundation
9500 Euclid Ave.
Cleveland, OH 44195, USA
Tel: +1 (216) 444 3642
Fax: +1 (216) 445 8475
e-mail: lowderc@cesmtp.ccf.org

Dr Krishna is currently affiliated with the University of Missouri–Kansas City, School of Medicine, Department of Ophthalmology/Eye Foundation, Kansas City, Missouri, USA

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The National Nosocomial Infections Surveillance System reports that *Candida* species are now the fourth most common nosocomial bloodstream pathogen.[1] Ocular candidiasis develops in 9–78% of candidaemic patients,[2–5] and risk factors or associations for development of ocular candidiasis in candidaemic patients include recent major surgery, drug abuse, bacterial sepsis, systemic antibiotic use, indwelling catheters, debilitating diseases, immunosuppression, prolonged neutropenia, organ transplantation or a combination of these factors.[6]

Ocular candidiasis results most commonly in chorioretinitis and endophthalmitis. Other ocular manifestations or complications of candidiasis may include iritis, choroidal neovascular membrane, 'string of pearls' vitreal opacities, or retinal detachment. *Candida albicans* and non-*albicans* species have been implicated as pathogens in the development of ocular candidiasis. Amphotericin B or azole[7] group antifungals may be used in the treatment of ocular candidiasis. Elective vitrectomy[8,9] can be performed to debulk infectious load, biopsy vitreous gel, remove scaffolding to prevent tractional complications, and allow greater penetration of antifungal agents in advanced cases with vitreal abscess or endophthalmitis.

The purpose of our study was to determine the length of ophthalmic follow-up required to rule out development of ocular candidiasis in hospitalised patients with candidaemia.

Materials and methods

A prospective observational study was conducted at the Cleveland Clinic Foundation between May 1996 and March 1997. The study was approved by the Cleveland Clinic Foundation Institutional Review Board. Personnel in the Department of Microbiology identified all adult (≥ 18 years old) candidaemic patients. Daily logs of these patients were reported to one investigator in the Division of Ophthalmology (R.K.) and one investigator in the Department of Infectious Disease (D.A.). Blood cultures were obtained during the study period using the BacT/Alert blood culture system (Organon Teknika, Durham, NC) using both aerobic and anaerobic bottles.

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Table 1. *Characteristics of 31 patients with candidaemia*

	n (%)
Male gender	17 (55%)
Mean age (years)	58 (range 33–82)
Intravascular devices	21 (68%)
⩾3 antibiotics	17 (55%)
Hyperalimentation	14 (45%)
Patients in intensive care unit at time of initial ophthalmological examination	11 (35%)
Diabetes mellitus	7 (23%)
Abdominal surgery within 30 days	7 (23%)
Systemic corticosteroids	7 (23%)
Immunosuppressive therapy	4 (13%)
Malignancy	1 (3%)

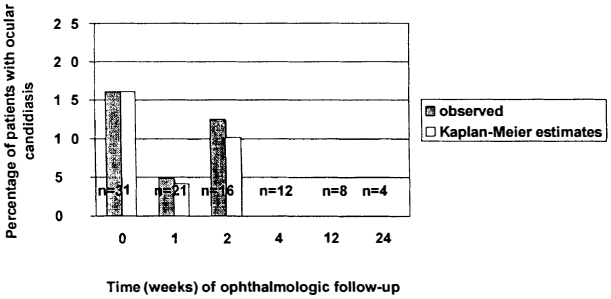

Fig. 1. *Graph of the observed incidence of ocular candidiasis from the onset of fungaemia and Kaplan–Meier estimates.*

Identification of *Candida* species was done using the Vitek YBC card system (bioMerieux, Hazelwood, MO).

Inclusion criteria for the study included all of the following: (1) candidaemia; (2) indirect ophthalmoscopy performed by one of the investigators (R.K., C.L.) within 72 h of notification of candidaemia; (3) no prior fungaemia; (4) life expectation ⩾ 72 h; and (5) informed consent.

Candida chorioretinitis was defined as a focal, white, infiltrative chorioretinal lesion with or without direct overlying vitreous haze. Endophthalmitis was defined as intravitreal fluff balls or vitreal abscess. The follow-up schedule for dilated ophthalmoscopy for patients without ocular candidiasis on initial examination was at 1, 2, 4, 12 and 24 weeks.

Data gathered included age, sex, risk factors for candidaemia, *Candida* species, interval from admission to candidaemia, duration of candidaemia, identifiable entry portal of *Candida*, and number of positive blood cultures for yeast. Data analysis was performed using Epi Info version 6 (Centers for Disease Control, Atlanta, GA). *p* values were determined using the Fisher exact test (two-tailed) and Wilcoxon rank-sum test when appropriate. Kaplan–Meier estimates were used to evaluate rates over the follow-up period.

Results

A total of 50 patients with candidaemia were identified at the Cleveland Clinic Foundation between May 1996 and March 1997, of whom 31 (62%) were included in the study. Among the patients excluded, 15 (30%) died before an initial ophthalmological examination could be performed, 2 (4%) refused to participate in the study, and 2 (4%) were discharged prior to the blood cultures becoming positive for *Candida*, which precluded an initial indirect ophthalmoscopic examination within 72 h.

Table 1 lists selected characteristics for the 31 study patients. *C. albicans* was the most common bloodstream isolate (15 patients; 48%) followed by *C. parapsilosis* (7 patients; 23%), *Torulopsis glabrata* (6 patients; 19%) and *C. tropicalis* (1 patient; 3%); 2 patients (6%) had polymicrobial fungaemias with *C. albicans* and *T. glabrata*. Twenty-two patients (71%) had an identifiable portal of entry for fungaemia: intravascular devices in 14 patients (45%), gastrointestinal tract in 5 patients (16%), genitourinary tract in 2 patients (6%) and prosthetic valve endocarditis in 1 patient (3%). The median interval from admission to onset of candidaemia was 11 days (range 0–40 days) and 55% of patients were candidaemic for ⩾ 2 days (range 1–27 days).

Table 2 details the characteristics of patients with ocular candidiasis in our study. The overall incidence of ocular candidiasis was 26% (8/31 patients); all manifested as chorioretinitis. No patient developed endophthalmitis or required ocular surgery. *C. albicans* was the pathogen in 6 of 8 patients (75%) with ocular candidiasis. Five patients (16%) had ocular candidiasis on their initial examination. One of 21 patients (5%) without ocular candidiasis on initial examination developed ocular candidiasis within 1 week. Two of 16 patients (13%) without ocular candidiasis on initial examination or at 1 week follow-up developed ocular candidiasis within 2 weeks. No evidence of ocular candidiasis occurred in the 12 patients with follow-up at 24 weeks (Fig. 1).

Table 2. *Characteristics of 8 patients with ocular candidiasis*

Patient no.	Age/Sex	Species	Ocular manifestation	Entry portal	Onset of diagnosis	No. of positive cultures	Treatment
1	48/M	*C. albicans*	Chorioretinitis	Line	Initial exam.	1	Amphotericin B
2	81/F	*C. albicans*	Chorioretinitis	Unknown	Initial exam.	4	Amphotericin B
3	56/M	*C. albicans*	Chorioretinitis	Line	Initial exam.	8	Amphotericin B/fluconazole
4	81/F	*C. albicans*	Chorioretinitis	Line	Initial exam.	2	Amphotericin B/fluconazole
5	73/F	*C. albicans*	Chorioretinitis	Endocarditis	Initial exam.	2	Amphotericin B
6	48/F	*C. albicans*	Chorioretinitis	Genitourinary	1 week	2	Amphotericin B/fluconazole
7	81/F	*T. glabrata*	Chorioretinitis	Unknown	2 weeks	1	Amphotericin B
8	65/M	*C. parapsilosis*	Chorioretinitis	Line	2 weeks	1	Amphotericin B/fluconazole

Table 3. *Comparison of 31 candidaemic patients with and without ocular candidiasis*

	Ocular candidiasis present (n = 8)	Ocular candidiasis absent (n = 23)	p value
Mean age (years)	63.6 ± 4.8	55.8 ± 3.5	0.29
Male gender	3 (38%)	14 (61%)	0.41
Intensive care unit at time of candidaemia	5 (63%)	6 (26%)	0.10
Intravascular device	5 (63%)	16 (70%)	1.00
Hyperalimentation	2 (25%)	12 (52%)	0.24
⩾ 3 antibiotics	4 (50%)	13 (56%)	1.00
Diabetes mellitus	0	7 (30%)	0.15
Abdominal surgery within 30 days	0	7 (30%)	0.15
Mean duration of fungaemia (days)	2.5	4.3	
Fungaemic > 2 days	3 (38%)	14 (61%)	0.41
Associated bacteraemia	5 (63%)	17 (74%)	0.66
Mortality	1 (13%)	9 (39%)	0.22

At the time of initial ophthalmological examination, all patients were receiving standard amphotericin B and/or fluconazole doses. All patients were maintained on an antifungal regimen until resolution of ocular signs. Nine patients (29%) died during the course of the study following the initial ophthalmological examination. Ill health, failure to return, or death prevented follow-up.

When we compared the 8 patients with ocular candidiasis with the 23 patients without ocular candidiasis, none of the variables assessed were significantly associated with an increased risk of ocular candidiasis (Table 3).

Discussion

Table 4 summarizes our results and previous reports of ocular candidiasis in patients with fungaemia. Our study is notable for the prospective longitudinal follow-up of patients with a negative examination at the time of screening. Ocular candidiasis occurred in 3 of 8 (38%) patients after a negative baseline examination: 1 at the 1 week follow-up examination and 2 at the 2 week follow-up examination. Similarly, Brooks[2] and Parke *et al.*[4] respectively reported 1 of 9 (11%) and 1 of 11 (9%) cases of ocular candidiasis occurring after an initial negative examination at 1 week follow-up. In our study,

Table 4. *Review of studies of ocular candidiasis in patients with fungaemia*

Authors, Year	No. of candidaemic patients	Species	Ocular candidiasis: n (%) and manifestation	Follow-up of negative patients	Ratio of patients who developed ocular candidiasis in follow-up to total number of patients with ocular candidiasis (%)
[Present report]	31	*C. albicans* 48% *C. parapsilosis* 23% *T. glabrata* 19% *C. tropicalis* 3% Other 1%	8 (28%) all chorioretinitis	1, 2 weeks; 1, 3, 6 months (when possible)	3/8 (38%)
Donahue *et al.*,[3] 1994	118	*C. albicans* 58% *C. tropicalis* 14% *T. glabrata* 14% *C. parapsilosis* 9% Other 1%	11 (9%) all chorioretinitis	None	
Brooks,[7] 1989	32	*C. albicans* 53% *C. parapsilosis* 22% *C. tropicalis* 3% Other 22%	9 (28%) all endophthalmitis	Weekly while in hospital	1/9 (11%)
Parke *et al.*,[4] 1981	38	*C. albicans* 72% *C. tropicalis* 13% *C. parapsilosis* 8% *T. glabrata* 5% *C. krusei* 3%	11 (29%) all endophthalmitis	5–7 days	1/11 (9%)
Henderson *et al.*,[10] 1981	9	*C. albicans* 100%	7 (78%) all endophthalmitis	Unknown	–
Griffin *et al.*,[5] 1974	82	Not available	9 (11%) all endophthalmitis[a]	None	–
Total	310	*C. albicans* 60% Non-*albicans* 40%	55 (18%)		5/28 (18%)

[a]Sixteen patients (20%) were found to have ocular candidiasis on post-mortem examination.

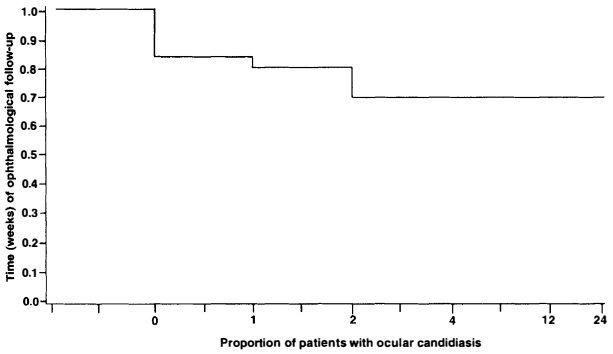

Fig. 2. *Kaplan–Meier analysis of the incidence of ocular candidiasis from the onset of fungaemia.*

the 3 patients who turned positive after an initial negative examination had similar clinical characteristics and a similar treatment course to the patients who were diagnosed with ocular candidiasis on initial examination. Blood cultures revealed *C. albicans* in the 5 patients who were diagnosed with ocular candidiasis on initial examination while the 3 patients who turned positive after initial negative examination cultured *C. albicans* (1), *Torulopsis glabrata* (1) and *C. parapsilosis* (1). The number of patients who turned positive after an initial negative examination is too small to make any conclusions as to whether the infecting organism has a role in the time to development of ocular infection. Kaplan–Meier analysis reveals that approximately 70% of patients will remain free of ocular candidiasis in the presence of candidaemia after 2 weeks of follow-up (Fig. 2).

In contrast to our findings where no patient had endophthalmitis, patients were described as having endophthalmitis in studies by Brooks,[2] Parke *et al.*,[4] Henderson *et al.*[10] and Griffin *et al.*[5] In a study by Donahue *et al.*,[3] strict criteria were used for classification of chorioretinitis and endophthalmitis; all cases of ocular candidiasis in their study manifested as chorioretinitis. Earlier diagnostic suspicion, examination and treatment may account for the decrease in severity of ocular candidiasis at initial presentation in our study, i.e. no patient had endophthalmitis or required surgery. Also, it is possible that endophthalmitis may have been present in the 15 patients who were excluded prior to initial examination due to severe morbidity and mortality. Barza[11] concludes that a long duration of antifungal treatment often suffices for chorioretinitis whereas marked vitritis requires vitrectomy and intravitreal injections.

The number of positive blood cultures has previously been correlated with a higher incidence of ocular candidiasis.[2,3] In our study we found that patients without ocular candidiasis had a higher mean number of positive blood cultures, but this was not statistically significant. Two of our patients with ocular candidiasis had only one positive blood culture. Parke *et al.*[4] reported that 6 of 10 patients with ocular candidiasis had only one positive blood culture.

We found an identifiable portal of entry in 22 of 31 (71%) patients. Two of 9 (22%) patients without an identifiable portal of entry developed ocular candidiasis – a similar percentage to the 6 of 22 (27%) patients who developed ocular candidiasis with an identifiable portal of entry. Rex *et al.*[12] found an identifiable portral of entry in 189 of 206 (92%) patients, but 83 of 206 (40%) were presumptive catheter tips. We do not routinely culture catheter tips, but it is likely that our remaining cases without an apparent source were catheter-related as well.

Fraser *et al.*[13] reported a mortality rate of 68% in untreated candidaemic patients. Griffin *et al.*[5] reported a 52% mortality within 3 months of a patient's first positive blood culture for *Candida*. In our patient population, 15 of 50 candidaemic patients (30%) died within 72 h of candidaemia identification. Nine of 31 patients (29%) included in the study also died. We may be underestimating the mortality rate in our study group due to loss of follow-up. We believe that the high rate of mortality is due to the high prevalence of co-morbidities.

There are several shortcomings in our study, including: (1) a small study population; (2) a lack of uniform follow-up and serial examinations (most of which were unavoidable due to patients' poor health, lack of longitudinal care at a tertiary care centre, and high mortality rate after baseline examination); and (3) the fact that 4 eligible patients were not examined. Nonetheless, Kaplan–Meier analysis does not reveal significant differences between observed and estimated rates of ocular candidiasis given the loss to follow-up and mortality (Fig. 1). Ocular microbiological confirmation was not possible because no patient required vitrectomy and biopsy in our study. However, bacterial endophthalmitis usually has a different clinical picture and does not typically resolve with intravenous antibiotics alone.

Ocular examination can aid in determining the presence of dissemination and thus guide in the assessment of duration of the treatment. Ocular candidiasis is often unrecognised or unassessed by the non-ophthalmologist and all candidaemic patients at our institution are routinely screened by an ophthalmologist. In an autopsy study by Edwards *et al.*,[14] 22 of 26 patients (85%) had tissue candidiasis if haematogenous ocular candidiasis was present.

In summary, a 2 week follow-up ophthalmological examination should be considered in candidaemic patients with a negative ophthalmological screening examination. The data from our study and the literature suggest that 9–38% of ocular candidiasis may be missed without a follow-up examination. In addition, all patients with ocular candidiasis in our study were maintained on systemic antifungal therapy until the disappearance of the ocular findings, whereas therapy may have been discontinued prematurely in the absence of continued ophthalmic follow-up.

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