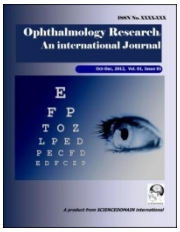

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A Retrospective Case Study of the Incidence of Endogenous Fungal Endophthalmitis in Patients with Positive Blood Cultures for Systemic Fungemia: Review of the Literature

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Authors' contributions

This work was carried out in collaboration between all authors. Author JC designed the study, managed the analyses, and helped write the first draft. Author KC managed the analyses of the study and wrote the first draft of the manuscript. Author LS helped with the literature search and wrote the final draft. Author SH designed the study, managed the analyses and oversaw all aspects of the study. All authors read and approved the final manuscript.

Original Research Article

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ABSTRACT

Aims: To determine the incidence of fungal ocular involvement, manifesting as chorioretinitis or endophthalmitis, in patients with positive fungal blood cultures in a tertiary care center.
Study Design: Retrospective case series and literature review.
Place and Duration of Study: Department of Surgery–Section of Ophthalmology and Visual Science, University of Chicago Pritzker School of Medicine, Chicago, Illinois. August 2006 to October 2009.
Methodology: Ophthalmology was consulted for evaluation of 100 adult and pediatric patients (47 men, 53 women; age range 10 days–84 years) with fungemia.
Results: Of 100 patients, blood cultures most frequently grew *Candida albicans* (42%), followed by *Candida parapsilosis* (22%), and *Candida glabrata* (16%). One patient had

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clinical signs of fungal ocular involvement (1/100, 1%) but no ocular symptoms. Blood cultures in this case were positive for *Candida glabrata*, and the patient clinically improved after switching antifungal therapy to PO voriconazole. Two other patients (2%) had nonspecific fundus lesions that were not consistent with chorioretinitis or endophthalmitis.
Conclusions: The incidence of ocular involvement in patients with fungemia is 1%, which is consistent with recent trends in literature. We believe that guidelines for screening criteria in at-risk inpatients for fungal chorioretinitis and endophthalmitis should be updated.

Keywords: Endophthalmitis; candidemia; fungemia; chorioretinitis; candida; vitritis.

1. INTRODUCTION

Fungal infections account for 9.5% of nosocomial blood stream infection in the United States [1]. Hospitalized patients are more vulnerable to systemic fungal infections, which can disseminate to the eye and lead to vision loss. Compared to other populations, they have more risk factors for fungal infection including broad-spectrum antibiotic use, recent major surgery, hyperalimentation, immune suppression, indwelling catheters, liver disease, diabetes mellitus, renal failure, intravenous drug abuse, and malignancy [2-13]. Disseminated fungal infection can present in the eye as chorioretinitis and/or vitreal infiltrates. If endophthalmitis is not treated, vitreoretinal abscesses with retinal necrosis, vitreous organization, and tractional retinal detachment may occur [8].

From 1972 to 1994, the incidence of endogenous fungal endophthalmitis in patients with systemic candidemia has ranged between 9%-40% [3,9,10,14,15]. Table 1 in the past, physicians were cautious in administering systemic antifungal therapy due to the concern over systemic toxicity. Recent literature suggests that the prevalence of disseminated ocular fungal infection has decreased, which may reflect physicians becoming less reluctant to initiate systemic antifungal therapy [16]. However, the guidelines in performing fundus exams on inpatients with systemic fungemia for ocular involvement have not changed.

This study provides an estimation of current prevalence of fungal ocular involvement in a hospital setting, the respective speciation of fungal infection, and risk factors in developing systemic fungal infection in hospitalized patients. In the setting of rising medical care costs and demand for inpatient consults, we believe that there needs to be updated guidelines and criteria in screening at-risk patients for fungal chorioretinitis and endophthalmitis.

2. METHODOLOGY

2.1 Study Center

Participants of this study were inpatients at the University of Chicago Medical Center in Chicago, IL. This study was approved by the Institutional Review Board prior to data collection.

2.2 Study Design

Clinical data were retrospectively collected at the University of Chicago Medical Center in which ophthalmology consults were requested to rule out ocular involvement in inpatients

with positive fungal blood cultures. A list of hospitalized patients with positive fungal blood cultures between August 1st, 2006 and October 31st, 2009 was compiled by the University of Chicago Microbiology Laboratory. Inpatient charts were reviewed to identify if ophthalmology was consulted for an eye exam within 24-48 hours after a positive fungal culture. Of the 217 in patients with culture-proven fungemia, 100 patients were examined by Ophthalmology.

Standard protocol of consult services at an academic institution was followed in this study. The primary team received an alert message to consult ophthalmology once a patient's blood culture was positive for fungal growth. The ophthalmologist saw the patient within 24-48 hours from the initial positive blood culture. Ophthalmologic examination consisted of a thorough history, visual acuity (when possible), external and anterior segment examination with a hand-held slit lamp, intraocular pressure with Tonopen, and dilated indirect ophthalmoscopy of both eyes.

Collected data included demographic information, visual symptoms, level of consciousness, ocular exam findings, fungal species identified in the blood culture, and antifungal therapy at time of eye examination. Risk factors for fungal dissemination were noted: recent major surgery, recent antibiotics therapy, indwelling catheters, hyper alimentation, immune suppression, malignancy, diabetes, etc. Exclusion criteria included patients without dilated exam at time of consultation, patients with history of ocular trauma, and patients with intraocular surgery within the past 30 days. Intraocular involvement in the eye is defined as either chorioretinitis, endophthalmitis, or both.

3. RESULTS AND DISCUSSION

Over a period of 38 months, 100 of 217 (46.1%) patients with systemic fungal infection were examined by the ophthalmology consult service. The remaining 117 (53.9%) of the patients with positive fungal blood cultures did not have a consult for ophthalmology evaluation placed during their hospitalization and were thus not evaluated. A total of 200 eyes from 100 patients were examined. The mean age of all patients examined was 44.3 years (10 days–84 years). Nineteen (19%) of the 100 patients were 18 years old or younger and 53 (53%) were female Fig. 1.

Candida species were the most common fungal organisms found in blood culture, accounting for 95% of all fungemia. The top 3 organisms accounted for 80% of the infections and consisted of *Candida albicans* (42%), *Candida parasilosis* (22%), and *Candida glabrata* (16%). Table 1 only one patient (1/100, 1%) had evidence of fungal endophthalmitis in our study. The affected patient was a 24 year-old female with cystic fibrosis who had vitritis without chorioretinitis and blood cultures that grew out *Candida glabrata*. She denied ocular symptoms. Her antifungal therapy was switched from IV fluconazole to PO voriconazole resulting in rapid clinical and subjective improvement.

At the time of ophthalmology examination, 96% of patients were receiving systemic antifungal therapy. Per hospital policy, initial systemic antifungal therapy consists of any of the following medications: micafungin 100mg IV daily, fluconazole 400mg PO/IV daily, amphotericin B 500mg IV daily, or a combination thereof. Most patients were on micafungin (33), followed by fluconazole (26), amphotericin (19), caspofungin (11), micafungin/fluconazole (7), and other/unknown (4).

The majority of patients (68%) did not have any ocular symptoms during examination. Of the 32 remaining patients, 10 patients complained of symptoms ranging from itching eyes to blurry vision, and 22 patients were not able to communicate their ocular symptoms due to their clinical condition (intubated, unconscious, or sedated at the time of examination) Table 2.

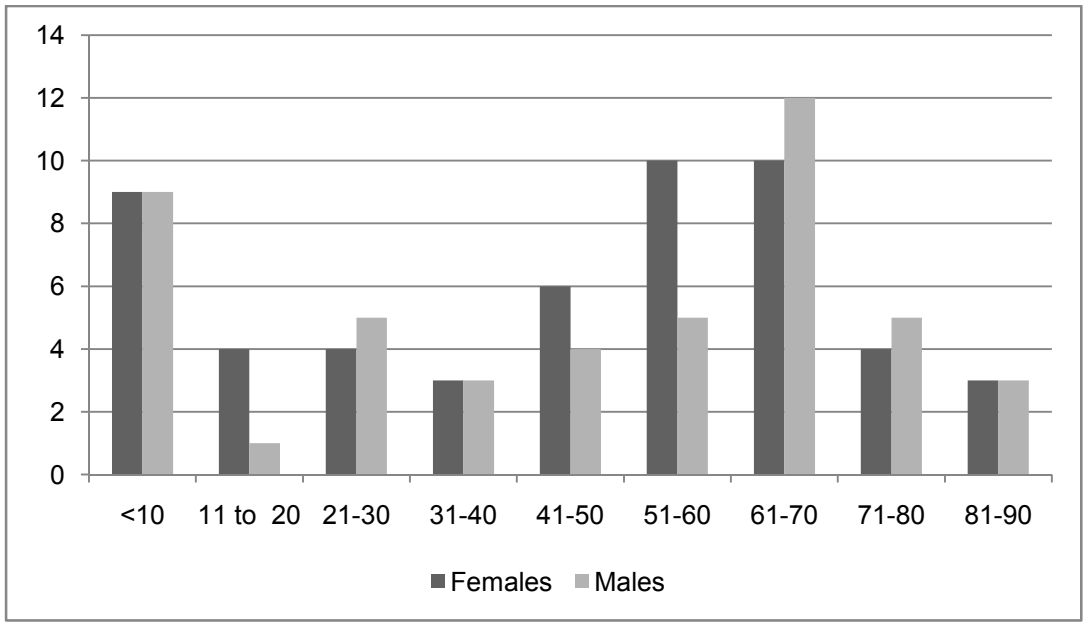

Fig. 1. Patient demographics stratified by age (in years) and gender (male or female)

Table 1. Speciation of fungal blood cultures

Organism	Number of patients
Candida albicans	42
Candida parapsilosis	22
Candida glabrata	16
Candida lusitaniae	6
Candida tropicalis	5
Yeast (unspecified)	4
Candida krusei	3
Cryptococcus neoformas	1
Candida albicans and *Candida glaberata*	1

Table 2. Ocular symptoms on presentation

Ocular symptoms	Number of patients
Blurry vision/Decreased vision/Itching	10
No ocular complaints	68
Unable to communicate ocular symptoms	22

The risk factors for development of endogenous fungal endophthalmitis in these patients included: history of recent antibiotic therapy (44%), immune suppression (16%), indwelling line (31%), and liver disease (8%). Other risk factors seen in 40% of patients consisted of short bowel syndrome, end stage renal disease, chronic heart failure, diabetes mellitus, recent surgery, or hyper alimentation. All patients (100%) had at least one risk factor Table 3.

Table 3. Risk factors for developing fungemia

Risk factors	Number of patients
Indwelling line	31
Immuno suppression	16
Recent antibiotic therapy	44
Liver disease	8
Other: SBS, ESRD, CHF, DM, recent surgery, TPN	40

SBS: short bowel syndrome, ESRD: End-stage renal failure, CHF: congestive heart failure, DM: diabetes mellitus, TPN: total parenteral nutrition

Two patients demonstrated significant posterior segment findings including chorioretinal scarring in one patient and bilateral small vitreous condensations with no chorioretinal lesions in another patient. Neither patient was diagnosed with fungal eye disease.

Miale reported the first case of hematogenous spread of Candida to the eye in 1943 [17]. Since then, endogenous fungal endophthalmitis has been described to be a relatively frequent complication of nosocomial systemic fungal infections. The incidence of fungal eye involvement has historically ranged from 9% to 40%, justifying the need for prompt eye examination in the setting of fungemia. However, more recently published incidence rates are <3%: Dozier 2011 <1%, Kannangara 2007 2.2%, Rodriguez-Adrian 2003 1% endophthalmitis and 2.7% chorioretinitis, Feman 2002 2.4%, and Scherer 1997 2.8% [18-22]. The incidence of 1% at University of Chicago Medical Center is in line with published incidence rates.

A few recent studies report significantly higher rates, notably in patients with candidemia. Krishna et al reported and incidence of 26% (8 of 31) of chorioretinitis in patients with fungemia, while Shah et al. [23,24] found 3 out of 28 (7.9%) patients had chorioretinitis. Oude Lashof et al. reported an incidence of ocular involvement of 16% and an incidence of endophthalmitis to be 1.6% in patients with candidemia. The significantly elevated incidence may be explained by the authors' definition of ocular involvement ("possible" versus "probable" cases), and the fact that it was a worldwide multicenter trial (incidence of fungal infection is higher in temperate climates) [2,25]. "Probable" ocular candidiasis, seen in 40 of 370 patients, was defined by inflammation, condensations in the vitreous or deep focal white infiltrates in the retina, and/or hemorrhages/Roth spots/cotton wool spots that were not explained by systemic diseases (i.e. hypertension and diabetes mellitus). "Possible" ocular candidiasis, seen in 20 of 370 patients, was defined by chorioretinitis in patients with underlying systemic diseases that can cause similar lesions.

The decrease in ocular involvement in patients with fungemia in the past decade could be explained by the prompt initiation of systemic antifungal therapy when a positive blood culture is reported and the overall improvement of medical care [16,22,26]. In the past, physicians were more hesitant to start systemic antifungal therapy due to concerns of

medication toxicity. Over the course of time this practice has changed, and in current practice, only one positive blood culture is required to start systemic therapy [16].

Candida species is the leading cause of invasive fungal infection in hospitalized patients in the United States and the most common cause of endogenous endophthalmitis [27,28]. Within the Candida species, *Candida albicans* is the most common of them all as supported in our study [2,11,22,27,29,30]. Our patient with fungal endophthalmitis had positive cultures for Candida glabrata and did not have any ocular symptoms. She was switched from IV fluconazole to PO voriconazole due to better ocular penetration. Other antifungals such as echinocandins do not achieve adequate therapeutic vitreous concentrations [31-34]. Other options in treating sight threatening cases include intravitreal injections of amphotericin B or voriconazole and/or vitrectomy [27,35]. These options were not pursued due to the patient's rapid clinical improvement.

Our study is limited by its retrospective nature and the fact that only 46.1% of217 patients with systemic fungal disease were evaluated by ophthalmology. Inpatient teams at our hospitals have different practices and do not always include an ophthalmology consult as part of workup after fungemia is discovered. Further research may reveal trends in consult practices; potential areas to examine include primary service specialty (surgical vs. medical), hospital length of stay, number and type of organisms found on blood culture, number of comorbid conditions, etc.

Patients who were examined and did not have any ocular findings of fungal infection did not receive serial exams after the initial consult examination. It is possible that they developed ocular involvement after the first eye exam, although we believe that this possibility is unlikely to change our incidence rate substantially. Some authors believe that ocular candidiasis is often asymptomatic and that retinal lesions are not always detected immediately after a positive fungal culture. They therefore recommend dilated fundus examination 1 week after initiating treatment [25]. However, Pappas et al showed that most cases (90%) of fungal endophthalmitis in non-treated patients develop within 72 hours of suspected onset of systemic fungal infection [15]. Of note, not all patients with positive fungal blood cultures received antifungal therapy and/or received an eye examination. Authors have suggested that positive blood cultures may represent skin contamination without fungemia, true but transient fungemia without infection, or local catheter colonization that resolves with removal of the device [14,21,29]. The decision to treat patients with fungemia not only depends on positive blood cultures, but also the clinician's index of suspicion for disseminated disease.

With the current standard of practice of treating systemic fungemia early, and a prevalence of disseminated ocular fungal infection of 1%, we recommend that the guidelines for consulting ophthalmology to rule out fungal eye disease be updated in an effort to reduce healthcare costs and to improve the efficiency of inpatient eye consult services. A study of ophthalmology inpatient consultations at a tertiary hospital in the United States, ruling out fungal involvement in the eye was the second most common primary ophthalmologic diagnosis request, behind refractive error [36]. This translates into significant resource expenditure for ruling out ocular fungal involvement.

Currently, the Infectious Disease Society of America recommends at least 1 dilated retinal examination early in the course of therapy, noting that it is especially important to examine patients who cannot communicate regarding visual disturbances [16]. The only patient in our study with endophthalmitis did not have visual symptoms. Similarly, Lashof et al. [25] noted

that of 60 patients with candidemia and fundoscopic abnormalities suggestive of endophthalmitis, the majority did not exhibit ocular symptoms and only 1 patient reported VA loss at baseline. However, the prevalence of symptoms varies widely, and Lingappan et al. reported visual symptoms in at least 77% of those patients with intravitreal culture-positive endogenous fungal endophthalmitis [27]. It is clear that a higher index of suspicion is necessary when patients present with visual complaints. Therefore, we propose that ophthalmologists preferentially examine patients with visual symptoms, patients who are critically ill (especially those in the ICU or with end-organ failure), or those who are unable to communicate their symptoms since they are correlated with ocular involvement in the setting of fungemia [24].

5. CONCLUSION

The incidence of ocular involvement in patients with fungemia is 1%, which is consistent with recent trends in literature. We believe that guidelines for screening criteria in at-risk inpatients for fungal chorioretinitis and endophthalmitis should be updated in an effort to reduce healthcare costs and to improve the efficiency of inpatient eye consult services.

CONSENT

A waiver of informed consent was obtained given that this study posed less than minimal risk to all participants and did not affect patient welfare.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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