
Ocular Involvement in Patients with Disseminated Fungal Infections

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ABSTRACT

Purpose: To evaluate ocular findings in hospitalized patients with suspected disseminated fungal infection and to suggest a reasonable protocol for requesting ophthalmology consultations on such patients. **Design:** Retrospective review of ophthalmological hospital consultations and literature review. **Results:** Of 149 consultations, five (3.4%) were to rule out ocular findings in patients with a culture proven disseminated fungal infection. Four similar retrospective reviews documenting 321 similar consults were discovered. Only seven (2.1%) of the 326 consults demonstrate fungal endophthalmitis. One hundred percent of these cases possessing adequate documentation reveal positive blood cultures and ophthalmic complaints (unless non-verbal) at the time of consultation. **Conclusion:** Fungal endophthalmitis has not been reported by the literature to occur in verbal patients lacking positive cultures and ophthalmic complaints. A safe, reasonable approach to ophthalmic consultations on verbal patients with suspected disseminated fungal infection is to limit such consultations to patients with both positive systemic cultures and subjective ophthalmic complaints.

INTRODUCTION

According to the Centers for Disease Control and Prevention, the third most common species isolated from healthcare-associated infections was *Candida spp*, with

Candida albicans being the sixth most common pathogen overall.¹ *Candida albicans* is also the most common organism associated with the development of endogenous endophthalmitis.² Outdated literature reports a strong association, as high as 45%,³ between disseminated fungal infection (DFI) and endogenous fungal endophthalmitis (EFE). Consequently, the Clinical Practice Guidelines for the Management of Candidiasis by the Infectious Diseases Society of America calls for ophthalmology consultations on all patients with candidiasis⁴ despite more recent reports of EFE occurring at rates below 3%.^{3,5,6,7} Due to these current and costly guidelines, an unnecessarily heavy burden on ophthalmologists has been established. A six-and-a-half year compilation of UCLA Medical Center and Neuropsychiatric Hospital ophthalmology consultations exposes the extent of this workload. The results of UCLA's study revealed that the consultation to "rule out fungal endophthalmitis" was their third most commonly requested consult and that "fungal endophthalmitis ruled out" was their second most common primary ophthalmological diagnosis.⁵ The disparity between suspected pathology and actual findings is striking.

Some have argued that the current protocol for ophthalmic consultations on all patients with DFIs is prudent due to the potentially disastrous effects of EFE on visual acuity. However, a recent study showed that *C. albicans* EFE was significantly associated with incorrect initial diagnosis, and revealed that a delayed correct diagnosis was not predictive of visual outcome, nor was initial treatment for an incorrect diagnosis of "uveitis."² This study suggests that waiting for patients to develop ophthalmic complaints, in respect to EFE, before requesting an ophthalmic consultation will not affect the visual outcome. Furthermore, the current literature does not appear to contain any reports of detectable EFE in verbal patients who were without subjective ophthalmic complaints at the time of their ophthalmic examination for EFE. Because of this, and reports that most consults to rule out EFE are for patients with no ocular complaints,³ it seems prudent that better guidelines be established to direct ophthalmic consultations for patients with DFIs. This paper attempts to suggest a safe

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Patient #	Reason for Suspicion	Ophthalmic Complaints	Abnormal Ophthalmic Findings
1	Positive cultures	None	None
2	Positive cultures	None (non verbal)	None
3	Positive cultures	None	None
4	Positive cultures	None	Moderate NPDR
5	Positive cultures	None (non verbal)	Twig branch Retinal artery occlusion

Regarding ophthalmology consultations for inpatients with disseminated fungal infections: The reason for a suspicion of fungal eye infection, any subjective or objective ophthalmic concerns by the patient and/or requesting physician, and ophthalmic findings made by the ophthalmology service are listed above.
NPDR: non-proliferative diabetic retinopathy

Risk Factor for Fungemia	Number of Patients
Chronic debilitation with indwelling catheterization	3
Total parenteral nutrition	1
Immunocompromised state	3
Broad spectrum intravenous antibiotics	4
Multiple risk factors	5

and logical approach to requesting ophthalmic consultations to rule out EFE in patients with DFIs through a retrospective review of ophthalmological hospital consultations and literature review of similar retrospective reviews specifically dealing with patients having suspected DFI.

METHODS

A retrospective review of all ophthalmic consultations that could be located from the period of July 2010 to January 2011 was performed by an ophthalmology service. These were random and there were no reasons to suspect they were biased toward a different rate of patients with positive findings. Chart records were evaluated further for patients whose consultation was to evaluate for ocular evidence of an endogenous fungal eye infection. The reason for a suspicion of fungal eye infection, any subjective or objective ophthalmic concerns by the patient and/or requesting physician, and ophthalmic findings made by the ophthalmology service were determined (Table I). A complete dilated fundus exam was performed on all consulted patients. Fundus findings were classified into one of four categories described by Donahue et al⁶ as follows:

Endophthalmitis was defined as a focal chorioretinitis with extension into the vitreous, intravitreal fluff balls, or vitreous haze associated with typical chorioretinal lesions. Chorioretinitis was defined as focal deep, white chorioretinal lesions with no evidence of direct vitreous involvement. "Nonspecific" fundus lesions were those associated with clear vitreous and no focal chorioretinitis. Patients with no lesions were categorized as normal.

The ophthalmic literature was also reviewed for "endogenous fungal endophthalmitis" using PubMed. A further review of the ophthalmic literature was done in: *American Journal of Ophthalmology*, *Survey of Ophthalmology*, *Ophthalmology Clinics*, and *British Journal of Ophthalmology*; key words included: endogenous endophthalmitis and fungal. Further, bibliographies were manually searched.

RESULTS

Of 149 consults seen over a seven month period, five were to rule out ophthalmic involvement in patients with DFI. None of the five patients had ophthalmic complaints at the time their consult was requested, however two were nonverbal and on ventilator devices. Each of the five patients had at least one positive fungal blood culture. None of the five patients had examination findings consistent with EFE or chorioretinitis. Three of the five patients were found to have normal eye exams. One patient was found to have a nonspecific retinal vascular finding of a twig branch retinal artery occlusion consistent with his history of multiple cerebrovascular events. One other patient was found to have moderate non-proliferative diabetic retinopathy consistent with his history of diabetes. Risk factors that appeared to predispose each of the five patients to a DFI was determined (Table II). These risk factors included chronic debilitation with indwelling catheterization in three patients, total parenteral nutrition in one patient, immunocompromised state in three patients, and broad spectrum intravenous antibiotic use in four patients. All five patients had more than one risk factor. No new predisposing risk factors for DFI not already published were identified.

A literature search resulted in four other papers over the last decade dealing with ophthalmological hospital consultations for patients with presumed DFI to rule out EFE. Institutions involved in these papers included the Retina Service of the Wills Eye Institute,⁷ the Departments of Ophthalmology and Visual Sciences and Pediatrics of Vanderbilt University School of Medicine,⁶ the Departments of Ophthalmology and Neurology and

Table III Each study's findings					
Consultations	Our Study	Retina Service of the Wills Eye Institute	Vanderbilt University School of Medicine	Saint Louis University Health Sciences Center	University of California Los Angeles School of Medicine and the Jules Stein Eye
All Consults	149	unknown	600	unknown	1472
For possible disseminated fungal infection	5	38	30	170	83
With positive systemic cultures	5	38	24	82	unknown
With subjective ophthalmic complaints at time of consult	0	1	unknown	10	unknown
With nonverbal patients at time of consult	2	2	unknown	unknown	unknown
With positive systemic cultures and ophthalmic complaints at time of consult or nonverbal	0	3	unknown	6	unknown
With fungal ocular findings	0	3	0	2	2
With fungal ocular findings but no positive cultures	0	0	0	0	unknown
With fungal ocular findings but no ophthalmic complaints in verbal patients	0	0	0	0	unknown
With fungal ocular findings and positive systemic cultures and subjective ophthalmic complaints or nonverbal	0	3	0	2	unknown
Percent of fungal ocular findings with both positive cultures and subjective ophthalmic complaints or nonverbal	unknown	100	unknown	100	unknown

Table IV Subjective ophthalmic complaints by patients found to have evidence of endogenous fungal endophthalmitis

- Blurred vision
- Floaters
- Flashes
- Red eyes
- Diffuse ache in one eye
- Multiple

the School of Medicine of the Saint Louis University Health Sciences Center,³ and the Department of Ophthalmology of the University of California Los Angeles School of Medicine and the Jules Stein Eye Institute.⁵ Out of these studies, and this one, a total of 326 ophthalmology consults were requested for patients with suspected DFI to rule out fungal ophthalmic involvement. Only seven patients, or 2.1%, were reported to have exam findings consistent with possible fungal ophthalmic involvement. Two of these seven were from a study that did not reveal any other information about the patients or their findings. 100% of the other five patients had positive blood cultures AND were either nonverbal or had subjective ophthalmic complaints (Table III). No documented cases of endogenous endophthalmitis were found from the literature search where patients were verbal and did not have subjective ophthalmic complaints

at the time of their examination. Subjective ophthalmic complaints by patients who were found to have examination findings consistent with EFE in these studies included blurred vision, floaters, flashes, red eyes, and diffuse ache in one eye (Table IV).

DISCUSSION

It is currently the standard of care for any patient with suspected DFI to have an ophthalmology consultation to rule out fungal ophthalmic involvement regardless of positive blood cultures and/or subjective ophthalmic complaints by the patient.⁴ This is striking as there does not appear to be any reported cases in the literature of patients with EFE who are verbal and without subjective ophthalmic complaints. Furthermore, every reported case of possible EFE from the studies reported above also had accompanying positive systemic fungal cultures. It has been postulated by multiple papers that the current low rates of EFE from patients with DFIs is due to our better understanding of DFIs and our ability for early treatment with effective antifungal medications.^{3,6,7} In lieu to these evidences, it seems reasonable that ophthalmic consultations for patients with suspected DFI should be limited to those patients who have positive systemic fungal cultures AND either have subjective ophthalmic complaints or are nonverbal or unreliable. This recommendation is further

supported by literature that showed a delay in diagnosis and treatment for *C. albicans* EFE was not predictive of visual outcome.² Therefore, it would be prudent to wait for reliable and verbal patients with positive systemic cultures with *C. albicans* and possible fungal ophthalmic involvement to become ophthalmologically symptomatic before requesting an ophthalmology consult.

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