ENDOPHTHALMITIS IN PATIENTS WITH DISSEMINATED FUNGAL DISEASE

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ABSTRACT

Background/Purpose: Fungal endophthalmitis caused by dissemination from extraocular fungal infections has been reported to vary between 9% and 45%. However, recent clinical experience disagrees with that. This study is an investigation of patients in an inner city teaching hospital, the risks associated with endogenous fungal endophthalmitis, and this incidence.

Methods: All ophthalmology consultations between February 1995 and August 2000 that might be associated with disseminated fungal infection were examined in a prospective manner. Patients were excluded if there was no evidence of a positive fungal culture from any site at any time. Visual symptoms were recorded along with ophthalmologic and systemic examination features. Information was gathered, including the identity of cultured organisms, the sites from which the organisms were obtained, and the patients' disposition.

Results: During this interval, 170 consultation requests contained the words "endophthalmitis" or "retinitis" and/or indicated concern about disseminated fungal infections. Extraocular fungal infections were found in 114 patients, but only 82 of them had evidence of systemic dissemination. Some patients had more than one organism. The following are listed in decreasing frequency of occurrence: *Candida albicans*, *Torulopsis glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, *Aspergillus niger*, and others. Only two patients had evidence of chorioretinitis and progressed to fungal endophthalmitis.

Conclusions: Endophthalmitis was rare among these patients with known fungal infections. Less than 2% had any related ophthalmic manifestations. Nevertheless, since treatment can save vision, evidence of intraocular infection should be sought as eagerly as before.

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INTRODUCTION

Endogenous fungal endophthalmitis (EFE) is a known complication of disseminated fungal infections. The frequency of EFE among patients with systemic fungal infections has been reported to vary between 9% and 45%.[1-5] Those accounts that used the most exacting criteria to identify EFE had the lowest frequency. One study of this type defined EFE as the "presence of deep white infiltrative chorioretinal lesions with extension of the surrounding inflammation into the vitreous or vitreous abscess manifesting as intravitreal fluff balls" and found a frequency of 9%.[1] Another study, which included autopsy data, reported that 11% of patients with disseminated fungal infections had ocular involvement.[2]

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Many different infections (eg, skin contamination, colonization of an intravenous catheter, blood-borne disease) can result in positive body fluid fungal cultures. Some may be limited to a particular site, while others may be widely disseminated. Because of the potential toxicity of antifungal therapy, it is in the patient's best interest to have proof of disease spread before starting systemic treatment. A common diagnostic method used for this in the past has been the ophthalmology consultation. Evidence of an endogenous intraocular fungal infection is a strong supporter of a decision to begin such therapy. However, the clinical practice patterns related to antifungal therapy may have changed. To better understand this, the frequency of EFE in hospitalized patients with positive fungal cultures was revisited.

STUDY DESIGN

The present study is an observational case series and case report. This information was accumulated, originally, as prospective patient evaluations. To satisfy institutional

review board requirements for patient and physician anonymity, however, this data collection was reexamined in a retrospective manner.

METHODS

In a prospective manner, at the time of the consultation, every "ophthalmology consultation service" report produced between February 1, 1995, and August 30, 2000, was entered into our research file. Appraisals were initiated whenever these records were found to contain the words "endophthalmitis" or "retinitis." Further investigation identified additional cases that included the term "fungal infection" or other phrases that could be related to a fungal infection in the consultation requests. Data analysis, however, was limited to those cases in which there was documentation of a positive fungal culture of any species from any source.

For statistical purposes, the following guidelines were used. Multiple requests for consultation made for a single patient during the same hospitalization were considered a single consultation request. When a consultation was requested for the same patient, but for a different hospital admission, the data was considered as a separate consultation.

Each patient's history was examined with a specific emphasis on the presence of ocular or visual symptoms, such as decreased vision, redness, pain, photopsias, or floaters. Medical histories were reviewed for data regarding comorbid diseases. Information collected included all signs of systemic infection and the results of the detailed ophthalmic examination. A slit-lamp biomicroscopic examination of the anterior segment of each eye was performed except when prevented by positioning concerns; in those cases, a penlight examination was conducted. All patients had dilated pupil indirect ophthalmoscopic examinations of their vitreous and retinas. The patients' laboratory test results were collected during the consultation sessions, which included information about the species and site of fungal organisms cultured. The *ICD-9* diagnoses for each patient were included in the file.

A patient was considered to have a superficial site of infection if the culture was taken from the urine, the intravenous catheter, a skin swab, or sputum. A patient was considered to have a systemic infection if the culture was taken from blood, bronchial wash, deep abscess, abdominal paracentesis, or thoracentesis.

In this study, the following definitions of chorioretinitis and EFE were used. Chorioretinitis was accepted as a diagnosis only when there was a deep white infiltrative chorioretinal lesion with no evidence of direct vitreal involvement. Endogenous fungal endophthalmitis, however, was limited to those cases in which there was evidence of (1) chorioretinitis with extension of the inflammation into the vitreous, (2) vitreous abscess manifesting as intravitreal fluff balls, or both.

RESULTS

During this interval, a total of 170 consultation requests were initiated because of concerns about disseminated fungal infections. Each consultation request was found to include the word "retinitis" or "endophthalmitis." However, only 114 of the patients were found to have had a positive fungal culture from any site at any time during that hospitalization. Of those patients, 82 (72%) had a positive systemic fungal culture, as defined, while 32 (28%) had no evidence of widespread systemic disease.

In this study, the population with positive fungal cultures from any site (114) had the following demographic features. Median age was 55 years (range, 15-84 years). There were 64 males (56%), and 82 patients described themselves as "white" (72%). All of the patients were severely ill, and almost half (about 46%) required artificial ventilation (endotracheal intubation) at the time of initial consultation.

The subpopulation with positive fungal cultures and evidence of systemic spread was similar to the total population described previously. This subpopulation consisted of 82 patients with a median age of 55 years (range, 15-84 years). There were 44 males (54%), and 59 of the patients described themselves as "white" (72%). The members of this subpopulation were severely ill with 28 (34%) intubated at the time the consultation requests were initiated.

The 32 patients who had positive fungal cultures from superficial sites had the following organisms identified in decreasing frequency: *Candida albicans*, *Torulopsis glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, *Candida lusitaniae*, *Aspergillus flavus*, unidentified yeast, and *Candida guilliermondii*. Some of these patients had coexisting ocular problems associated with such disorders as diabetes mellitus, hypertension, and age-related macular degeneration. Of the 32 patients in this group, four complained of recent onset of visual symptoms, two described blurred vision, and two had "redness" in one eye. In addition, 12 had retinal findings. Six patients had new cotton-wool spots, four had local areas of "dot-blot" hemorrhages, one had a round "white-centered" hemorrhage, and one had a small, localized area of serous retinal detachment. If any systemic fungal infection had been present, these findings might have been interpreted as part of an intraocular fungal infection. However, since fungal dissemination was not present in any of these cases, these abnormalities must represent features of coexisting ocular disorders.

Most of the patients with positive fungal cultures from a systemic infection site had no visual symptoms. However,

a few complained of the following: three had "red eyes," two described floaters and blurred vision, and one had a diffuse "ache" in one eye. Although most had no ophthalmic abnormalities detected by examination, two patients had chorioretinitis as defined previously, and both developed intravitreal "fluff balls." In addition, three patients had hard exudates, three had local areas of dot-blot hemorrhages, two had new cotton-wool spots, one had perivascular sheathing, one had retinal pigment epithelial atrophy, and one had an area of subretinal neovascularization. One of the patients with fungal endophthalmitis complained of redness, foreign body sensation, and blurred vision in his left eye. He was found to have keratic precipitates, 3+ anterior chamber cells, posterior synechiae, cells in the vitreous, multifocal sites of chorioretinitis, and a fluff ball in the vitreous at the time of the ophthalmic examination.

Those patients with positive fungal cultures from systemic sites had the following organisms identified in decreasing frequency: *C albicans*, *T glabrata*, *C tropicalis*, *C parapsilosis*, *C krusei*, *Aspergillus niger*, *C lusitaniae*, *C norvegensis*, *Histoplasma*, *Alternaria*, *Aspergillus fumigatus*, *Cryptococcus*, *Curvularia*, unidentified fungus, *Geotrichum capitatum*, *Histoplasma capsulatum*, *Mucor*, *Mycobacterium avium*, *Mycobacterium tuberculosis*, *Penicillium*, *Pneumocystis*, *Saccharomyces cerevisiae*, and *Trichosporon beigelii*.

Some type of ophthalmic abnormality was found in approximately 17% of all patients who had a positive systemic fungal culture. However, chorioretinitis was identified in only two of these infected patients. Both patients with chorioretinitis progressed to fungal endophthalmitis. In short, fungal endophthalmitis occurred in only 2 of the 82 patients (2.4%) who had evidence of disseminated infection. The following case report describes the clinical features of one of the endogenous fungal endophthalmitis patients.

CASE REPORT

A 46-year-old man with a history of insulin-dependent diabetes mellitus, hypertension, and chronic hepatitis C infection was hospitalized. He had end-stage cirrhotic liver disease and was identified as a potential recipient of an organ donation. While being evaluated for a possible liver transplantation, he had several episodes of intestinal bleeding; each required hospitalization for transfusions and treatment. During one admission, he was found to have a prostate abscess infected with *Candida*. This was treated with an incision and drainage procedure and systemic therapy with fluconazole, 200 mg intravenously every 24 hours. Blood cultures were positive for *C albicans* for 3 days after the start of therapy, but the cultures were negative thereafter.

Ten days after the abscess incision and drainage, he complained of redness, foreign body sensation, and blurred vision in his left eye. Visual acuity was 20/20 with each eye. The anterior segment and vitreous of the right eye were normal, while the left eye had 2+ cell and flare, 180° of posterior synechiae, and 2 to 3+ vitreous cell. Multifocal areas of chorioretinitis were seen scattered throughout the posterior pole of each eye. The systemic antifungal therapy was increased by the addition of amphotericin B, 45 mg intravenously every 24 hours, and flucytosine, 2,250 mg orally every 12 hours. Most of the chorioretinal lesions regressed during the next 30 days. However, when the systemic regimen was reduced, his visual acuity became worse and the lesions in the left eye were found to be enlarged (Figure 1). A pars plana vitrectomy was then performed to clear the vitreous cavity. At the end of the surgical procedure, a total of 5 µg of amphotericin B dissolved in 0.1 mL of saline was injected into the vitreous cavity. The material removed from his vitreous was cultured for bacteria and fungi. No organisms grew from these specimens, and the patient's condition rapidly improved.

Six months after the operation, the patient's visual acuity was 20/20 in each eye. The only residual findings were some pigmentary changes at the level of the retinal pigment epithelium.

DISCUSSION

The present study finds a much lower frequency of EFE in hospitalized patients with positive fungal cultures than previously reported.[1-5] When compared to the publications with the strictest definition of EFE, our data indicate a reduction in frequency.[1] EFE occurred in only 2 of the 82 patients (2.4%) who had evidence of disseminated disease.

It is our belief that fungal sepsis is being identified and treated earlier in its course as a consequence of greater understanding of the disease and the adverse effects of antifungal therapy. Therefore, EFE and chorioretinitis are

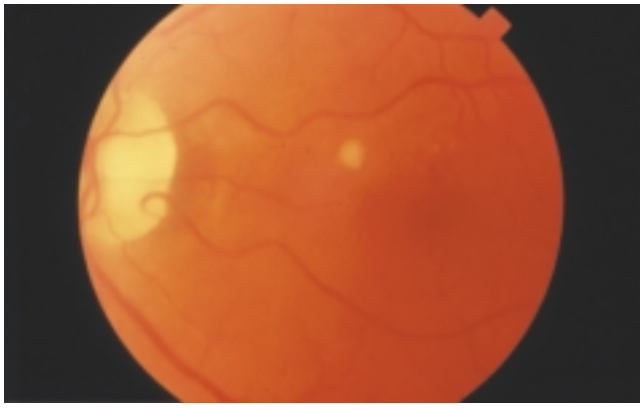

FIGURE 1
Left eye of patient with endogenous fungal endophthalmitis 25 days after systemic therapy with amphotericin B and flucytosine was begun.

being prevented because the fungemia origination sites are being treated earlier in the course of the disease process. As a corollary, however, this means that those few patients with evidence of EFE are at a great risk of harboring those infectious agents that are insensitive to their current medical therapies.

We are unaware of previous literature on EFE or chorioretinitis in patients with superficial sites of positive fungal culture. We found no EFE or chorioretinitis among the 32 patients that had only superficial fungal infections. Although we report on a small sample size, we believe that patients with a positive fungal culture from a superficial site are at very low risk for intraocular infections. If future larger studies confirm this trend, then there could be no need for ophthalmology consultations when a patient has a positive fungal culture from a superficial site.

It is important to emphasize that our findings should not be misinterpreted. The enthusiasm with which one seeks intraocular fungal infection, and the practice patterns associated with ophthalmic consultations in patients with fungal disease, should not be affected by this report. The discovery of EFE and its prompt treatment could be an organ-saving or lifesaving event. Because current therapies work so well, physicians need to maintain a constant vigil for disorders that are not sensitive to standard medical regimens. That was why a vitrectomy, along with procedures to culture and test the vitreous contents for drug sensitivity, was appropriate for the patient described in the case report.

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DISCUSSION

DR WILLIAM TASMAN. Dr Feman and his coworkers looked at all ophthalmology consultations seen between February 1995 and August 2000 that might be associated with systemic fungal infection. Eighty-two such patients were identified and the most common organism was *Candida albicans*. Their article then goes on to provide evidence that the frequency of ocular manifestations in systemic fungal infection is probably less than 2%, a finding that differs with reports of higher frequencies ranging anywhere from 9% to 45%.[1-5]

Clearly, fungal endophthalmitis under any circumstance is rare. In a review of 95 endophthalmitis cases seen by our practice during the calendar year 2001, most were postoperative and none had a fungal etiology. The last fungal endophthalmitis that I personally saw prior to last year was a case of *Candida parapsilosis* and that was in a patient who developed bilateral infection secondary to cataract extraction on both eyes.

Interestingly, however, so far in 2002 an endophthalmitis patient with hepatitis C was seen on the Retina Service of Wills Eye Hospital with disseminated *Candida albicans* infection. Consultation was also requested for another *C albicans* patient with intraocular involvement emanating from an intravenous catheter.

One of the two patients identified out of the 82 in Dr Feman's series was a 46-year-old man who had a history of insulin dependent diabetes, hypertension, chronic hepatitis C infection, and endstage cirrhotic liver disease. Predisposing factors for fungal infection include intravenous catheters, bowel surgery, corticosteroid therapy, intravenous drug use, and diabetes. In addition, a recent article in the *Archives of Ophthalmology* documented *Candida* endophthalmitis in an asplenic patient after tattooing.

A few years ago we conducted a study to see if diabetics were more prone to postoperative endophthalmitis after cataract surgery than nondiabetics. Of 162 consecutive patients treated over a 5-year period for endophthalmitis that occurred within 2 weeks of ocular surgery, 21% were diabetic. I therefore asked Dr Feman if his second affected patient had any other associated conditions that might increase the risk of fungal infection such as diabetes or an intravenous catheter. With access to more information about patient No. 2, a 48-year-old Caucasian female with acute lymphocytic leukemia, Dr Feman informed me that she was not diabetic. Although she had a vascular access device implanted as part of her cancer chemotherapy, it had been removed a few days before eye consultation was requested.

I would like to congratulate the authors on presenting evidence that the frequency of eye findings in disseminated fungal disease is probably lower than we had previously thought.

DR DAN B JONES. David Parke's prospective study in 1982 indicated a much higher incidence of fundus lesions (about 29%). A retrospective study by Howard Cupples found fundus lesions occurred in about 2%, similar to today's

presentation. In Dr Parke's study, they acted upon the report from the laboratory of a positive fungal blood culture. Most of the patients were not on treatment and only one was really immunosuppressed with corticosteroid therapy. Almost all were associated with *Candida albicans* with 10 having endophthalmitis, retinitis, or advancement to the vitreous. Why the discrepancy? Whether it's 29% or 2%, I think that the bottom line is the same–that you must respond to a positive fungus blood culture. Over that same period of time, how many other patients had *Candida* positive blood cultures in your hospital? With that, one could determine how often the primary physicians did not request ophthalmology consultations. Then we would know if there has been a change in consultation request patterns.

DR JULES L. BAUM. There might be a correlation with the interval between onset of the patient's systemic symptoms and the initiation of systemic therapy. A delay in systemic therapy might relate to the incidence of fungal endophthalmitis.

DR STEPHEN S. FEMAN. I'll answer Dr Baum's question first. We had similar concerns at our referral center, since some patients were from outside hospitals. Therefore, the interval between symptom onset and therapy initiation may be inexact in some cases. However, in each case where it was well documented, systemic medical therapy was started in less than 24 hours.

Dr Jones raised a question about the change in incidence of this disorder. The literature and Dr Parke's paper, were well known when this study started. The difference between Dr Parke's paper and the clinical experience at my medical center was what initiated our questions. Since then, it was found that our hospital's Internal Medicine and Systemic Infectious Disease experts begin treatment earlier in the disease process, when compared to Dr Parke's paper. That is, antifungal therapy is started when blood cultures are obtained, and before their results are known. This may be why the classic ocular features rarely develop and the incidence of endogenous fungal endophthalmitis (EFE) is less.

Dr Tasman was helpful in his early communications to me. It is interesting to know that in 2001, among the 95 cases of endophthalmitis at the Wills' Eye Hospital, there was no fungal disease. However, in 2002, although the data are incomplete, one case was seen and consultation was requested on another.

In light of these comments, it is important to emphasize that this should not affect our search for intraocular fungal infection. The discovery of EFE and its prompt treatment could be an organ-saving or lifesaving event.