Aspergillus Endophthalmitis
An Unrecognized Endemic Disease in Orthotopic Liver Transplantation

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Purpose: The authors discovered an unusually high incidence of Aspergillus endophthalmitis in an autopsy series of orthotopic liver transplantation recipients. This study was conducted to discern the frequency, topographic distribution, and potential significance of the infections.

Methods: Autopsy reports from liver transplant patients were reviewed. All patients with Aspergillus endophthalmitis were studied by gross and histologic examination. Histologic sections were stained with Grocott-Gomori methenamine-silver nitrate and periodic acid-Schiff stains. Some Grocott-Gomori methenamine-silver nitrate stained sections were counterstained with hematoxylin-eosin. The distribution of ocular infections in the eye was determined for each patient. The organs infected were determined at autopsy.

Results: The authors found seven patients with Aspergillus endophthalmitis. Six of these seven patients were from a group of 85 (7.1%) orthotopic liver transplantation recipients. Fourteen (16.5%) orthotopic liver transplantation recipients had invasive pulmonary aspergillosis and ten (11.8%) had disseminated disease. The eyes were the second most common site of infection. Two patients had ocular involvement as the only nonpulmonary site of infection. Aspergillus endophthalmitis was diagnosed in only one patient before death. Infection was located posterior to the equator in all patients; three patients were anterior to the equator as well. The retina (5/7), vitreous (5/7), and choroid (3/7) were common sites of infection.

Conclusions: This is the first report of Aspergillus endophthalmitis associated with orthotopic liver transplantation recipients. Patients with orthotopic liver transplants are unusually susceptible to invasive aspergillosis and Aspergillus endophthalmitis. Aspergillus infection is frequently bilateral, begins posteriorly in the retina or choroid, and has vitreous involvement. Recognition of this entity is important because many patients die of disseminated Aspergillus infection that may be detected early with bedside fundusscopic examination. Ophthalmology 1996;103:757-767

Invasive fungal infections are an important cause of morbidity and mortality in immunosuppressed patients. Those most at risk for developing infection from Aspergillus species are patients who are intravenous drug users1 and patients who are immunosuppressed, including recipients of organ transplants,2,3 individuals infected with

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Definitions of Aspergillus Infections

Aspergillus species are a ubiquitous group of saprophytic fungi and an important cause of human fungal infection. The name Aspergillus is derived from the microscopic appearance of the spore-forming structure (asper meaning rough and gillus meaning head).

Aspergillus has been reported to cause invasive infection in 1.5% of patients receiving liver transplants. Pulmonary infection was the most common manifestation and was found in 29 (1.3%) of 2180 patients. No patients with Aspergillus endophthalmitis were reported in this series.

Forty well-documented reports of patients with endogenous Aspergillus endophthalmitis have been noted in the literature, 25 of whom were examined histologically. Reported in the literature are four orthotopic renal transplant recipients, one bone marrow transplant recipient, one orthotopic heart transplant recipient, and one orthotopic lung transplant recipient. Aspergillus endophthalmitis has not been reported in a liver transplant recipient. We report the autopsy findings of seven patients who had endogenous Aspergillus endophthalmitis, which occurred in six after orthotopic liver transplantation (OLT).

Materials and Methods

Study Population

The study population included patients with Aspergillus endophthalmitis, OLT, or both, drawn from 2500 autopsies at our institution from 1984 to 1995.

Gross and Microscopic Examination

Eyes were fixed in 10% formaldehyde solution or 4% paraformaldehyde for a minimum of 48 hours, washed in buffer or water, and transferred to 50% ethanol. Eyes were examined macroscopically according to previously described methods. At least one eye of patients with gross findings consistent with fungal infection was examined histologically. Sections were stained with hematoxylin-eosin, periodic acid-Schiff, and Grocott-Gomori methenamine-silver nitrate stains. Characteristic septate hyphae with dichotomous branching at 45° angles and culture identification were considered diagnostic of Aspergillus infection.

We performed a search of the literature for all patients with endogenous Aspergillus endophthalmitis. The following criteria were used for inclusion in our study: (1) intraocular culture with growth of Aspergillus species; (2) the presence of typical organisms in the uveal tract, retina, vitreous cavity, or anterior chamber in conjunction with a positive culture from a nonocular source; or (3) clinical presentation consistent with fungal endophthalmitis with a positive culture from a nonocular source. Patients were not included in the study if they had a history of recent penetrating trauma, fungal keratitis, or spread of infection from contiguous structures.

Results

EIGHTY-FIVE patients with OLTs were identified. Forty-eight were women, and 37 were men. The median age of all patients was 46 years (range, 7 months to 75 years). There were nine children younger than 10 years of age.

Fourteen of the 85 patients (16.5%) had invasive Aspergillus infection. Eight were women, and six were men. The median age was 50 (range, 30–63 years). Pulmonary infection was present in each patient. Disseminated disease was found in ten (11.8%) patients. The organs infected with Aspergillus are listed in Table 1. The findings in all patients with ocular involvement were documented histologically. Some of the nonocular sites of infection were identified at autopsy by gross features of Aspergillus infection according to previously described findings.

All 14 subjects had antemortem cultures from the respiratory tract that grew Aspergillus species. In one patient, vitreous, bile, and respiratory cultures grew Aspergillus species. Another patient had growth from respiratory and wound cultures. The average time from obtaining a culture, which subsequently grew Aspergillus species, to death was 6 days (median, 5 days) in ten patients for whom data were available. Dichotomously branched septate hyphae were documented histologically in at least one eye.

Table 1. Sites of Infection in 14 Patients with Invasive Aspergillus

<table>
<thead>
<tr>
<th>Organ</th>
<th>No.* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Eyes</td>
<td>6 (42.9)</td>
</tr>
<tr>
<td>Heart</td>
<td>5 (35.7)</td>
</tr>
<tr>
<td>Kidney</td>
<td>5 (35.7)</td>
</tr>
<tr>
<td>Brain</td>
<td>4 (28.6)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Liver</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Stomach</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Spleen</td>
<td>2 (14.3)</td>
</tr>
</tbody>
</table>

* Number of patients with gross or microscopic infection.
Hunt and Glasgow • Aspergillus Endophthalmitis

of eight patients. One did not have growth of Aspergillus species in culture, and the records could not be obtained for another. They, therefore, did not meet our criteria for inclusion in the endophthalmitis or invasive disease group.

The median age of the remaining six patients was 50 years (range, 35–63 years). Four were women, and two were men. The eyes were the second most common organs infected (Table 1). In two patients, the eyes were the only organs found to be involved other than the lungs. Four patients with disseminated disease did not have gross ocular lesions. Two had histologic sections made that did not show any infecting organisms.

Endophthalmitis antemortem was diagnosed in only two of the six patients. Endophthalmitis developed in one patient while that patient required amphotericin B therapy for invasive pulmonary aspergillosis. She had a positive vitreous culture for Aspergillus species and was treated with intravitreous amphotericin B. The other patient did not have cultures performed before death, and Candida endophthalmitis was misdiagnosed clinically in the patient. Endophthalmitis developed in one patient with invasive pulmonary aspergillosis and Candida sepsis. However, the infecting organism in the eye could not be determined because histologic sections were not available.

Histologically proven Candida endophthalmitis was not found in these 85 patients. Nineteen of the 85 patients had positive antemortem cultures for Candida, at least 13 of whom were treated with amphotericin B. Eight patients had Candida cultured from the blood. Five patients with invasive aspergillosis had positive cultures for Candida as well. Other fungal isolates (all treated) included Coccidioides immitis (2 patients), pseudo-Allesheria boydii (1 patient), and Scedosporium apiospermum (1 patient). None had endophthalmitis.

The hepatic diseases leading to transplant for the three groups of patients (those with OLT, with invasive disease, and with endophthalmitis) are listed in Table 2. There were no significant differences among the groups regarding the underlying hepatic disease.

Only one patient was identified from the autopsy records with Aspergillus endophthalmitis who did not have OLT. Disseminated fungal disease and endophthalmitis developed in one eye after heart transplantation. In another patient, endophthalmitis developed, which was caused by a fungus with septate dichotomously branched hyphae. He had a history of chronic obstructive pulmonary disease and chronic steroid use, and disseminated aspergillosis with bilateral endophthalmitis developed in the patient. No record was available to confirm infection by Aspergillus species.

Of the seven patients with histologic confirmation of Aspergillus endophthalmitis, three had gross lesions in the fellow eye. Thus, there was a total of ten eyes with Aspergillus endophthalmitis. Right and left eyes were affected equally.

Gross retinal lesions associated with infecting organisms consisted of intraretinal hemorrhages, including white-centered hemorrhages, preretinal hemorrhages, subretinal hemorrhages, shaggy white perivascular, and large confluent exudates (Fig 1). Two eyes had retinal detachment. Isolated choroidal lesions were characteristically discrete, white, and sometimes elevated (Fig 1). Combined retinal and choroidal lesions were common. The vitreous showed diffuse haziness, discrete condensations in the cortical vitreous, or both and sometimes mild hemorrhage. In three eyes, the vitritis was dense enough to obscure the view of the underlying retina and choroid.

The topographic distribution of gross lesions is shown in Figure 2. All ten infected eyes had involvement of at least part of the postequatorial fundus. No eyes had gross lesions of the pre-equatorial fundus without involvement of the postequatorial fundus. The inferotemporal quadrant was most commonly involved. The fundus temporal

### Table 2. Major Diseases Leading to Orthotopic Liver Transplantation

<table>
<thead>
<tr>
<th>Disease</th>
<th>All Transplant Recipients</th>
<th>Invasive Aspergillus Infection</th>
<th>Aspergillus Endophthalmitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients (%)</td>
<td>No. of Patients (%)</td>
<td>No. of Patients (%)</td>
</tr>
<tr>
<td>Infectious</td>
<td>23 (27)</td>
<td>8 (57)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Alcohol related</td>
<td>19 (22)</td>
<td>4 (29)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Biliary atresia</td>
<td>6 (7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>6 (7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sclerosing cholangitis</td>
<td>5 (6)</td>
<td>1 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>5 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>5 (6)</td>
<td>0 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>3 (4)</td>
<td>2 (14)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Others</td>
<td>14 (16)</td>
<td>3 (21)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Total*</td>
<td>85</td>
<td>14</td>
<td>6</td>
</tr>
</tbody>
</table>

* Some patients have more than one etiology.
to the optic nerve was more likely to be involved than was the nasal side (10 versus 7).

The histologic findings of the seven patients with endophthalmitis are presented in Table 3. Sections did not show fungal organisms in the anterior chamber of any patient. One patient did have a dense, fluffy-white, organized exudate adherent to the anterior iris, which was composed of a mixture of acute and chronic inflammatory cells and cellular debris. All other eyes had an infiltration of lymphocytes and plasma cells in the iris stroma to a varying degree.

Retinal lesions were angiocentric. Hyphae infiltrated the lumen, vessel wall, and surrounding tissues (Fig 1). Thrombosed vessels were common and, in some areas, were devoid of infecting organisms. Acute and chronic inflammatory cells infiltrated the infected areas. Granulomata contained rare giant cells. Hemorrhage in all retinal layers was frequent. A large sublaminar abscess was present in the macula of one eye (Fig 1).

Choroidal infection was characterized by angiocentric invasion and a variable amount of mixed acute and chronic inflammatory response (Fig 1). Hemorrhage in the choroid was less common and less extensive. Inflammatory cells and edema sometimes caused thickening of the choroid. Mild diffuse infiltration of lymphocytes and plasma cells was common in uninfected choroid.

Usually, retinal and choroidal lesions were contiguous. However, one eye showed a discrete focus of choroidal infection without involvement or reaction of the overlying retinal pigment epithelium or retina. This focus was not associated with any gross findings. Likewise, there were areas of retinal infection with no corresponding infection of the choroid. Hyphae often spread on the surface of Bruch membrane without penetration.

Vitreous infection was found in all eyes with retinal lesions. Vitreous inflammation was composed predominately of acute inflammatory cells. Occasionally, small, discrete abscesses were present (Fig 3). Lymphocytes and macrophages surrounded fungal hyphae.

Ciliary body infection did not occur in any of the patients with culture identification. It was found in one patient with dichotomous branching of septal hyphae and was associated with contiguous fungal vitritis. The pars plana and the tips of several ciliary processes were engulfed by the dense vitreous infection.

Optic nerve infection did not occur in any of the patients with culture identification. One patient had several thrombotic disc vessels in one eye but no fungi. No inflammation or thrombosis was found posterior to the lamina cribrosa in five eyes with sections through the optic nerve. Optic nerve head vessels were infected by typical fungi in one patient with characteristic hypthal morphologic. Scleral infection was found in one eye, which was contiguous with adjacent choroidal infection.

Table 4 lists all patients with endogenous *Aspergillus* endophthalmitis who were identified from the literature. There were 40 patients who met our criteria for inclusion. Several other reports identified *Aspergillus* species as the infecting agent that did not meet our criteria.

### Discussion

The association of OLT and *Aspergillus* endophthalmitis has not been reported previously. Our data suggest that endogenous *Aspergillus* endophthalmitis results from spread of infection from other organs.
Aspergillus endophthalmitis has not been recognized clinically in three series of OLT recipients.\textsuperscript{2,57-58} There are several possible reasons. Disseminated aspergillosis is usually fatal and endophthalmitis occurs often in obtunded patients unable to communicate visual symptoms.

In addition, \textit{Aspergillus} organisms are difficult to isolate from blood cultures. A positive blood culture has not been reported in a patient with \textit{Aspergillus} endophthalmitis. In contradistinction, positive blood cultures are common in \textit{Candida} endophthalmitis and prompt ophthalmologic consultation. In one series, 53\% of patients with \textit{Candida} endophthalmitis had positive blood cultures.\textsuperscript{59} Lack of awareness of \textit{Aspergillus} species as a cause of endogenous fungal endophthalmitis may lead to misdiagnosis of \textit{Candida} infection if vitreous cultures are not performed. This was the case in one of our patients who was treated presumptively for \textit{Candida} but was proved subsequently at autopsy to have \textit{Aspergillus} endophthalmitis.

The detection of endophthalmitis in our population compared with previous studies of OLT may reflect the fact that autopsy eyes are examined routinely at our institution. The condition of six of seven patients in our series were diagnosed only at autopsy. Furthermore, we may have underestimated the number of patients because two more patients who did not meet our criteria for inclusion likely had disseminated aspergillosis and endophthalmitis.

The high prevalence of \textit{Aspergillus} endophthalmitis also may be due to a higher rate (16.5\%) of invasive aspergillosis compared with rates of other series of liver transplantation recipients (1.5\% to 5.0\%).\textsuperscript{2,58,60} The rates of infection for previous studies on OLT recipients are listed in Table 5. Unlike our study, these reports were clinical and autopsy series. As in our study, invasive pulmonary disease was the most common infection.\textsuperscript{2,60} Disseminated disease was found in 0.7\% of all patients or 16 (50\%) of 32 of those with invasive disease in their series, whereas it was found in 11.8\% of all patients or 10 (71\%) of 14 of those with invasive disease in our series. However, other authors report a similar incidence of invasive aspergillosis (16.7\%) and disseminated disease (66.7%).\textsuperscript{57}

Our patient population is drawn from autopsies of OLT recipients. However, this does not reflect the true prevalence of invasive aspergillosis at our institution. One possible explanation for the discrepancy in incidence of invasive aspergillosis among various studies is an environmental factor predisposed to infection. Of the 13 OLT recipients who died in the last 12 months of the study, 8 (61.5\%) had invasive aspergillosis. This clustering of patients was investigated, and \textit{Aspergillus} organisms were found in the air ducts and patient care spaces. Extensive cleaning resulted in lower organism counts. Patients were relocated to a different ward as well. These measures were instituted too recently to assess their effect on infection rates. Consistent isolation of \textit{A. fumigatus} also suggests a local environmental exposure in our patients. However, we doubt this is an endemic infection specific to our institution because similar rates have been found in previous studies,\textsuperscript{57} and infection in our most recent patient was caused by \textit{A. nidulans}.

Liver transplant recipients are more prone to fungal infections than are other organ transplant recipients. This may be because of a common defect in phagocytosis.\textsuperscript{61,62} \textit{Candida} has been reported to be two to six times more common than is \textit{Aspergillus} infection in OLT recipients.\textsuperscript{57,63} We noted only a slightly greater number of \textit{Candida} infections (\( n = 19 \)) than of \textit{Aspergillus} (\( n = 14 \)). However, there was a much greater incidence of endophthalmitis caused by \textit{Aspergillus} than by \textit{Candida}. The reasons for this are unknown.

In a series that did not include liver transplant recipients, McDonnell found that endophthalmitis developed in 2 (8.3\%) of 26 patients with invasive aspergillosis and that all of these patients had multiple organs involved.\textsuperscript{26} None were detected clinically before death. Endophthalmitis developed in nearly 11 (12\%) of 94 patients with \textit{Candida} infection. The eyes were the fifth most common organ system involved with \textit{Candida} infections. Similar

### Table 3. Histologic Sites of Infection in Seven Eyes with Aspergillus Endophthalmitis

<table>
<thead>
<tr>
<th>Tissue</th>
<th>1*</th>
<th>2*</th>
<th>3*</th>
<th>4*</th>
<th>5*</th>
<th>6*</th>
<th>7†</th>
<th>Total</th>
<th>Literature†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior segment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Ciliary body</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Choroid</td>
<td></td>
<td>-</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>Retina</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NP</td>
<td>5</td>
</tr>
<tr>
<td>Vitreous</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NP</td>
<td>5</td>
</tr>
<tr>
<td>Optic nerve</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NP</td>
<td>0</td>
</tr>
<tr>
<td>Sclera</td>
<td>-</td>
<td>-</td>
<td>NP</td>
<td>NP</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

NP = tissue not present in available sections.
* Orthotopic liver transplant recipient.
† Orthotopic heart transplant recipient.
‡ Twenty-five well-documented cases of \textit{Aspergillus} endophthalmitis with histologic findings.
analysis was not reported for *Aspergillus* infections. In our study, the eyes were the second most common organ system involved and endophthalmitis developed in two patients as the only nonpulmonary site of infection at autopsy. Our data suggest that there is a greater risk of endophthalmitis developing in patients with OLT with disseminated aspergillosis than in patients with disseminated candidiasis. At least 13 (68%) of 19 patients with invasive candidiasis and 9 (64%) of 14 patients with invasive aspergillosis in our series were treated with amphotericin B. The absence of *Candida* endophthalmitis in these patients may reflect successful eradication of infection.

One reason for the lack of success in treatment of *Aspergillus* infections is the difficulty in making early diagnosis. In ten patients, we were able to determine that an average of 6 days had elapsed between culture procurement and death. Ocular infection was present in a significant percentage of patients with invasive disease. The actual duration and progression of ocular infection are not known. Some lesions were focal with minimal destruction of adjacent tissue, suggesting recent ocular infection. We could not correlate the extent of ocular lesions with duration of disease. It is possible that earlier recognition in some patients may improve the ultimate outcome.

We found that gross signs of *Aspergillus* infection occurred posterior to the equator in every patient, which would be expected to cause visual symptoms. These findings are consistent with those of case reports of *Aspergillus* endophthalmitis in other clinical settings. Visual symptoms should be ascertained from all patients at risk for disseminated aspergillosis. In patients unable to report visual symptoms, frequent direct funduscopic examination by nonophthalmologists would detect most posterior lesions of *Aspergillus* endophthalmitis.

It has become increasingly evident that in patients who are debilitated, positive cultures for *Aspergillus*, especially respiratory isolates, are likely to indicate invasive disease rather than simple contamination. Therefore, ophthalmologic consultation is indicated in patients with OLT with visual symptoms, pulmonary infiltrates, or respiratory cultures that grow *Aspergillus*. Our patients with invasive disease had growth of *Aspergillus* species in sputum or tracheal aspirate cultures. Only two had cultures positive for *Aspergillus* from nonrespiratory sites. Vitreous biopsy would be indicated to confirm the diagnosis of *Aspergillus* endophthalmitis after initiation of appropriate therapy for systemic disease. Vitreous cultures were positive in 23 (92%) of 25 patients reported in the literature (Table 4).

Anterior chamber infection is rare and has been reported as an isolated site of infection only twice in previously reported patients with *Aspergillus* endophthalmitis. Inflammation, hypopyon, or organized exudates are not uncommon. Only one eye in our series had significant inflammation in the anterior chamber, which was characterized by an organized exudate on the iris surface. Multiple sections failed to show organisms. Only one of four anterior chamber aspirates was positive in patients previously reported with *Aspergillus* endophthalmitis. Therefore, aqueous cultures are likely to be inadequate in *Aspergillus* endophthalmitis, even when severe anterior chamber inflammation is present.

Ocular aspergillosis produces occlusive vasculitis in the retina and choroid. Hyphae cause obstruction and thrombosis, penetrate the vessel walls, and infect surrounding tissue and contiguous structures, such as the sclera and vitreous. Tissue damage results from direct invasion and by secondary infarction.

*Aspergillus* may be angiotrophic. The hyphae proliferate within walls and appear concentrated near vessels. In some areas, we found a dense concentration of hyphae within the retina over vessels. Hyphae emanated from the vitreous and were less numerous in areas devoid of vessels. The branched orientation suggests daughter hyphae are oriented toward vessels and may represent growth toward nutrients.

Lesions in our series involved the choroid, retina, and vitreous together. This pattern of infection confounded identification of the initial site of infection in most areas.
Table 4. Reported Cases of Endogenous Aspergillus Endophthalmitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Medical History</th>
<th>Eye</th>
<th>Vitreous Culture*</th>
<th>Aqueous Culture*</th>
<th>Organism†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graham et al11</td>
<td>OLT T</td>
<td>OS</td>
<td>NP</td>
<td>NP</td>
<td>(Aspergillus fumigatus)</td>
</tr>
<tr>
<td>Coskuncan et al8</td>
<td>BMT</td>
<td>OD</td>
<td>+</td>
<td>NP</td>
<td>Aspergillus flavus</td>
</tr>
<tr>
<td>Katz et al13</td>
<td>Asthma/steroids</td>
<td>OD</td>
<td>NP</td>
<td>–</td>
<td>(A. fumigatus)</td>
</tr>
<tr>
<td>Valluri et al14</td>
<td>None</td>
<td>OD</td>
<td>+</td>
<td>NP</td>
<td>A. fumigatus</td>
</tr>
<tr>
<td>van den Anker et al15</td>
<td>Prematurity</td>
<td>Unilateral</td>
<td>–</td>
<td>NP</td>
<td>(A. fumigatus)</td>
</tr>
<tr>
<td>Gross16</td>
<td>IVDA</td>
<td>OS</td>
<td>+</td>
<td>NP</td>
<td>Aspergillus terreus</td>
</tr>
<tr>
<td>Kalina and Campbell17</td>
<td>CLL</td>
<td>OD</td>
<td>NP</td>
<td>–</td>
<td>(A. terreus)</td>
</tr>
<tr>
<td>Barr et al18</td>
<td>IVDA</td>
<td>Unilateral</td>
<td>+</td>
<td>NP</td>
<td>A. flavus</td>
</tr>
<tr>
<td></td>
<td>IVDA</td>
<td>Unilateral</td>
<td>+</td>
<td>NP</td>
<td>A. flavus</td>
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<tr>
<td>Bodoia et al10</td>
<td>OHT</td>
<td>OU</td>
<td>NP</td>
<td>NP</td>
<td>(A. fumigatus)</td>
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<td>OS</td>
<td>+</td>
<td>NP</td>
<td>A. fumigatus</td>
</tr>
<tr>
<td>Weiss et al16</td>
<td>ORT</td>
<td>OU</td>
<td>+</td>
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<td>A. fumigatus</td>
</tr>
<tr>
<td>Lance et al20</td>
<td>IVDA</td>
<td>OD</td>
<td>+</td>
<td>NP</td>
<td>A. flavus</td>
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<tr>
<td>Halperin and Roseman21</td>
<td>IVDA</td>
<td>OD</td>
<td>+ (a)</td>
<td>NP</td>
<td>A. flavus</td>
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<td>Jampol et al22</td>
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OLT T = orthotopic lung transplant; OS = left eye; NP = not performed; BMT = bone marrow transplant; OD = right eye; IVDA = intravenous drug abuse; CLL = chronic lymphocytic leukemia; OHT = orthotopic heart transplant; OU = both eyes; ORT = orthotopic renal transplant; AML = acute myelogenous leukemia; RCS = reticulum cell sarcoma; NA = not available; IPT = idiopathic primary thrombocytosis; ABPA = allergic bronchopulmonary aspergillosis, CMV = cytomegalovirus.

* (+) = positive; (−) = negative; (a) = culture from subretinal abscess; (b) = culture performed on vitreous from enucleation or postmortem specimen.
† Culture results in parentheses are from a nonocular source.
‡ Sputum culture result from 2 1/2 months before positive vitreous culture; species of vitreous culture are not reported.
§ Aqueous culture with mixed infection: A. flavus and Torulopsis glabrata.
In contrast, Candida endophthalmitis begins predominantly in the choroid.\textsuperscript{58} Just like other investigators, we found that organisms frequently align themselves along anatomic barriers to spread, such as Bruch membrane and the internal limiting membrane. We found no involvement of the optic nerve posterior to the lamina cribrosa. Infection of the optic nerve posterior to the lamina cribrosa associated with endophthalmitis is rare.\textsuperscript{17,34} Table 3 lists the sites of infection from patients in the literature. Vitreous and retinal infection were the most common and tended to occur together. The choroid was the third most common site.

Three of seven of our patients had bilateral endophthalmitis. Left and right eyes were infected equally in patients with monocular disease (2 each). Sihota reported that left eyes were three times more likely to be involved in monococular endogenous \textit{Aspergillus} endophthalmitis and that this was explained by the more direct route of the left ocular circulation from the aorta.\textsuperscript{43} Our review showed that in 10 patients the right eye only was involved, in 14 the left eye only was involved, and in 9 there was bilateral involvement. Bilateral endophthalmitis has not been reported in an intravenous drug user. Dissemination in these patients probably represents a \textit{one-hit} mechanism rather than a continuous seeding as would be expected in other forms of disseminated infection. In this group, right eyes were infected in five patients compared with four with left eye involvement. This does not support circulatory architecture as an important factor in determining the laterality of infection.

The differential diagnosis of fungal endophthalmitis in patients with OLT includes \textit{Candida}, \textit{Coccidioides}, and \textit{Aspergillus}. All patients had lesions in the postequatorial fundus. Important differences exist in the posterior disease that may help distinguish them clinically. \textit{Candida} lesions are usually small (<1 mm in diameter) focal, choroidal lesions and are less likely to have associated retinal hemorrhage.\textsuperscript{58} Ocular coccidioidomycosis presents almost exclusively as either anterior or posterior uveitis.\textsuperscript{64} The most common posterior lesions are discrete choroidal granulomas (0.5–2.0 mm in size), which are usually separate from retinal granulomas.\textsuperscript{55} Retinal hemorrhage is uncommon. Extensive retinal hemorrhage, large confluent patches of infection, or both strongly suggest a diagnosis of \textit{Aspergillus}.

\textit{Coccidioides immitis} was the third most common fungal infection in our population. It has been considered an important infection in other liver transplant centers, probably because of their geographic location. Endophthalmitis did not develop in any patient in our series. This disease must be considered in these patients who are immunocompromised.

The most striking difference in the pathogenesis of \textit{Aspergillus}, \textit{Candida}, and \textit{Coccidioides} endophthalmitis is the predilection for vascular infection. Although these three fungi are disseminated through vascular channels,\textsuperscript{59,65} \textit{Aspergillus} infects the blood vessels directly and causes thrombosis and infarction.

Both \textit{A. fumigatus} and \textit{A. flavus} have been isolated from OLT recipients. In our series, \textit{A. fumigatus} was isolated in six patients and \textit{A. nidulans} in one patient. This is consistent with the findings of Kusne et al,\textsuperscript{2} who found \textit{A. fumigatus} in 87% of patients having liver transplantation with pulmonary invasion. The other 13% grew \textit{A. flavus}. Two patients with invasive intra-abdominal aspergillosis also grew \textit{A. fumigatus}. Conversely, Castaldo found \textit{A. flavus} in six of seven positive cultures and none with \textit{A. fumigatus}.\textsuperscript{57} This clustering of species lends support to the local hospital environment being the important factor leading to infection rather than differences in species virulence.

\textit{A. fumigatus} was isolated in 18 (75%) of 24 previously reported patients with endophthalmitis who were nonintravenous drug users. In contrast, \textit{A. flavus} was isolated in 10 (83%) of 12 reported patients with \textit{Aspergillus} endophthalmitis who were intravenous drug users. Other species of \textit{Aspergillus} are rarely isolated, reflecting either lower virulence or the relative distribution of species in the environment. Ours is the first reported patient with endophthalmitis caused by \textit{A. nidulans}. The species of all reported patients are listed in Table 4.

We report seven patients with \textit{Aspergillus} endophthalmitis; six of these patients had OLT. This infection was unrecognized previously in this patient population. Based on our data, we recommend careful, daily, bedside, funduscopic examination of all hospitalized patients with OLT by the attending service. Retinal and choroidal lesions occur near the macula, allowing for easy visualization. Ophthalmologic consultation is recommended for patients with OLT with visual symptoms, fever of unknown origin, chest x-ray findings consistent with pulmonary aspergillosis, and those with \textit{Aspergillus} species cultured from sputum. Unique clinical features provide for differentiation from other fungal causes of endophthalmitis in some patients. The systemic distribution of infections is such that results of ocular examination may

Table 5. Comparison of Rates of Dissemination and Endophthalmitis between Three Liver Transplant Populations

<table>
<thead>
<tr>
<th></th>
<th>Kusne et al\textsuperscript{2}</th>
<th>Castaldo et al\textsuperscript{57}</th>
<th>Singh et al\textsuperscript{58}</th>
<th>Current Study</th>
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<tr>
<td>No. of patients</td>
<td>2180</td>
<td>72</td>
<td>55</td>
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<td>Patients with invasive aspergillosis (%)</td>
<td>32 (1.5)</td>
<td>12 (16.7)</td>
<td>3 (5.5)</td>
<td>14 (16.5)</td>
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<tr>
<td>Patients with disseminated aspergillosis (%)</td>
<td>16 (50.0)</td>
<td>8 (66.7)</td>
<td>3 (100)</td>
<td>10 (71.4)</td>
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<tr>
<td>Patients with Aspergillus endophthalmitis (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6 (42.9)</td>
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</table>
aid early detection and subsequent treatment of disseminated aspergillosis.

References


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