A COMPARATIVE CLINICOPATHOLOGIC STUDY OF ENDOGENOUS MYCOTIC ENDOPHTHALMITIS: VARIATIONS IN CLINICAL AND HISTOPATHOLOGIC CHANGES IN CANDIDIASIS COMPARED TO ASPERGILLOSIS*

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ABSTRACT

Purpose: Endophthalmitis caused by endogenous *Candida* and *Aspergillus* species has emerged as a visually threatening complication in patients with immune deficiency of various causes. Twenty-five patients who underwent enucleation, 13 with endogenous *Aspergillus* endophthalmitis and 12 with endogenous *Candida* intraocular infections, were evaluated. Both clinical features and intraocular spread of the fungi were studied to determine which clinical and/or histopathologic features could help distinguish aspergillosis from *Candida* infections.

Methods: Clinical information was sought from each case to determine whether there was any underlying systemic condition and to delineate the characteristic clinical features seen at initial presentation. The results of vitreous and other tissue cultures for bacteria and fungi were evaluated. Patients with AIDS were excluded. The enucleated globes were processed for histopathologic analysis to detect location of the fungal elements, inflammatory response, and vascular invasion by the fungi.

Results: With respect to the various predisposing systemic conditions, *Candida* species endophthalmitis was noted in patients with a history of gastrointestinal surgery, hyperalimentation, or diabetes mellitus, whereas aspergillosis was present in patients who had undergone organ transplantation or cardiac surgery. The vitreous was the primary focus of infection for *Candida*, whereas subretinal or sub–retinal pigment epithelium infection was noted in eyes with aspergillosis. Retinal and choroidal vessel wall invasion by fungal elements was noted in cases of aspergillosis but not in cases with candidiasis. The high rate of cerebral and cardiac infection in patients with *Aspergillus* endophthalmitis was not seen in those with *Candida* infection.

Conclusions: The present study indicates that unlike *Candida* endophthalmitis, aspergillosis is seen in organ transplant or cardiac surgery patients, and its initial clinical presentation includes extensive areas of deep retinitis/choroiditis. Contrary to the findings in *Candida* endophthalmitis, vitreous biopsy may not yield positive results in aspergillosis. *Aspergillus* endophthalmitis is usually associated with a high rate of mortality caused by cerebral and cardiac complications.

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INTRODUCTION

Endogenous fungal endophthalmitis has emerged as a visually threatening complication in intravenous drug abusers and in patients with immune deficiency of various etiologies. In immunocompromised patients, intraocular infection represents dissemination of invasive diseases due to *Candida* species, *Aspergillus* species, *Fusarium* species, *Cryptococcus neoformans*, *Pseudallescheria boydii*, and other organisms.[1-11] Among these, *Candida* species is the most common, followed by *Aspergillus* infection.[12]

Clinically, host factors such as parenteral hyperalimentation, gastrointestinal surgery, hematologic malignancies, organ transplantation, and immunosuppressive therapy have been reported to predispose patients to the development of endogenous fungal endophthalmitis.[1-15] The histopathologic changes in the various fungal infections have been documented in individuals with these predisposing host factors.[16-18] Most of these studies have been isolated case reports suggesting the occurrence of *Candida* endophthalmitis in association with such predisposing host factors as hyperalimentation, gastrointestinal surgery, corticosteroid therapy, and lymphomas, whereas aspergillosis has been found in organ transplant recipients and those

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with granulocytopenia.[16-28] Moreover, it appears that *Candida* species have a predilection for invasion of the vitreous, whereas *Aspergillus* preferentially invades the retina and choroid. Furthermore, retinal and choroidal vascular invasion with resulting infarction appears to be a predominant feature in *Aspergillus* endophthalmitis, but not in *Candida* intraocular infections.[1-8]

Although the clinical features of both *Candida* and *Aspergillus* intraocular infections have been described in detail, the clinical features and histopathologic changes that occur with these 2 fungal infections have not been correlated to delineate characteristic clinical and histopathologic changes that could help distinguish *Candida* infections from aspergillosis.

In the present study, we evaluated the clinical features and patterns of intraocular fungal invasion in cases of fungal endophthalmitis to determine those distinguishing features that may be helpful in clinically differentiating between *Candida* infections and aspergillosis. Furthermore, an attempt is made to address the factors that play a role in the preferential growth of *Candida* in the vitreous and *Aspergillus* in the retina and choroid.

MATERIALS AND METHODS

Enucleated globes from patients with a diagnosis of endogenous fungal endophthalmitis caused by disseminated *Candida* or *Aspergillus* infection were obtained from the files of the Armed Forces Institute of Pathology and the Ophthalmic Pathology Laboratory of the Doheny Eye Institute. Patients with acquired immunodeficiency syndrome and cases with mycotic endophthalmitis due to perforating ocular injuries or corneal ulcers were excluded. Cases of endophthalmitis caused by other mycotic organisms were rare and were excluded.

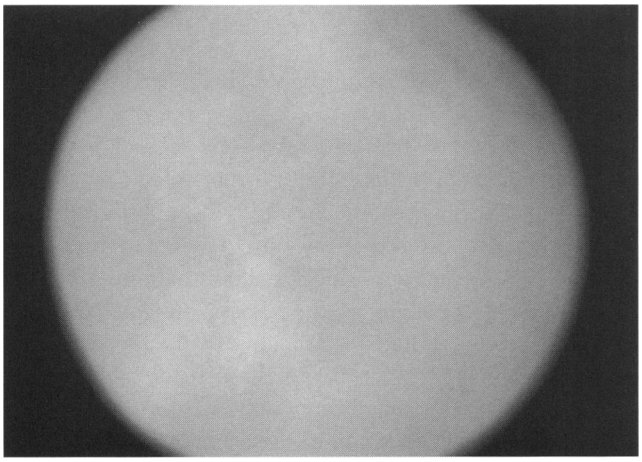


FIGURE 1
Fundus photo of case 22 showing retinitis and vitreous exudate. Retinitis was diagnosed clinically as acute retinal necrosis.

Histopathologically, acute endophthalmitis was characterized by the infiltration of polymorphonuclear leukocytes into the vitreous cavity with the inflammatory process involving retina and/or uvea as well. Special stains, including periodic acid–Schiff (PAS), Gomori-methanamine silver (GMS), and a combination of PAS, GMS, and Gridley fungal stains were used to confirm the presence of the infectious agent. In selected cases, alcian blue and mucicarmine were used.

The globes were examined to detect the type of inflammatory process: acute suppurative, chronic nongranulomatous, or granulomatous. Location of the fungal elements was determined using sections stained with PAS and GMS. Clinical information was sought from each case to determine the clinical features at initial presentation and any underlying systemic condition such as abdominal surgery, hyperalimentation, organ transplantation, immune suppression, diabetes, malignancies, or treatment with multiple antibiotics or systemic corticosteroids and/or cytotoxic agents. The results of vitreous and other tissue microbial cultures for bacteria and fungi were evaluated.

RESULTS

A total of 25 patients were identified; 13 had endogenous *Aspergillus* endophthalmitis, and 12 had endogenous *Candida* intraocular infection. Demographic features and underlying systemic diseases are summarized in Table I. The median age of patients with *Candida* infection was 60 years, with a mean age of 56 years and a range of 20 to 83 years. In patients with aspergillosis, the median age was 48 years, with a mean age of 45 years and a range of 24 to 79 years. Both infections were more common in men than in women (Table I). There were 11 men and 1 woman in the candidiasis group and 9 men and 4 women in the aspergillosis group.

Patients initially presented with diagnoses of granulomatous anterior uveitis, vitritis, vitreoretinitis, panuveitis, chorioretinitis, or endophthalmitis (Table II). Only 1 case of *Aspergillus* endophthalmitis presented with clinical features of a granulomatous anterior uveitis. Vitritis or vitreoretinitis was diagnosed in 7 patients with *Candida* infection and 2 patients with aspergillosis. A diagnosis of chorioretinitis was reported in 2 cases of aspergillosis. Two other patients with aspergillosis presented with clinical features suggestive of acute retinal necrosis (Fig 1). Three patients with *Candida* infection and 2 patients with aspergillosis presented with clinical findings of panuveitis. Endophthalmitis was a presenting feature in 4 cases of aspergillosis and in 2 cases of candidiasis (Table II).

Conditions preceeding the development of fungal endophthalmitis included gastrointestinal surgery or

TABLE IA: CLINICAL SUMMARY OF 12 CASES WITH ENDOGENOUS CANDIDA ENDOPHTHALMITIS

CASE	AGE	SEX	SYSTEMIC CONDITION	INTRAOCULAR INFLAMMATION		EYES ENUCLEATED AT	
				UNILATERAL	BILATERAL	SURGERY	AUTOPSY*
1	69	M	Abdominal Surgery complicated by pyelonephritis	OD	-	+	-
2	41	M	Abdominal Sx for intestinal fistula	OS	-	+	-
3	75	M	Diabetes, Lymphoma	OS	-	+	-
4	56	M	Hyperalimentation, indwelling catheter	OS	-	+	-
5	70	M	Abdominal Sx for small bowel fistula	OS	-	+	-
6	33	M	Abdominal Sx for duodenal ulcer	OS	-	+	-
7	20	M	Abdominal Sx for ulcerative colitis	OS	-	+	-
8	60	M	Diabetes, epiglottis carcinoma	OS	-	+	-
9	83	M	Diabetes	OD	-	+	-
10	73	M	Not known	OD	-	+	-
11	23	M	Pneumonia treated with triple antibiotics	OD	-	+	-
12	75	F	Temporal arteritis treated with corticosteroids		+	-	+

* Case 12 autopsy revealed a large cerebral abscess containing *Candida*.

TABLE IB: CLINICAL SUMMARY OF 13 CASES WITH ENDOGENOUS ASPERGILLUS ENDOPHTHALMITIS

CASE	AGE	SEX	SYSTEMIC CONDITION	INTRAOCULAR INFLAMMATION		EYES OBTAINED AT		AUTOPSY FINDINGS*
				UNILATERAL	BILATERAL	SURGERY	AUTOPSY	
13	61	M	Coronary artery bypass & rheumatic disease	OS	-	-	+	Brain, heart
14	26	M	Wegener's vasculitis treated with cyclophosphamide	OD	-	+	-	
15	30	F	Renal transplant	-	+	-	+	Brain, heart, Lung, thyroid, GI
16	37	F	Renal transplant	OD	-	+	-	
17	48	M	Renal transplant	-	+	-	+	Not available
18	52	M	Renal transplant	-	+	-	+	Brain, heart, lung
19	79	M	Aortic valve replacement	-	+	-	+	Brain, heart, lung
20	39	M	Aortic valve replacement	-	+	-	+	Heart
21	60	F	Immunosuppression from chronic steroid treatment	OS	-	+	-	
22	58	M	Aortic valve replacement	-	+	-	+	Brain, heart
23	24	F	SLE, treated with corticosteroids, methotrexate; pancytopenia	OS	-	+	-	
24	37	M	Alcoholic cirrhosis	OD	-	-	+	Brain
25	59	M	Sarcoidosis & chronic obstructive lung disease; treated with corticosteroids	-	+	-	+	Brain, heart

SLE, systemic lupus erythematosus.
* Presence of Aspergillus in the organs on histologic examination.

TABLE II: INITIAL CLINICAL PRESENTATION OF ENDOGENEOUS FUNGAL ENDOPHTHALMITIS IN 25 CASES

DIAGNOSIS	*CANDIDA*	*ASPERGILLUS*
Granulomatous anterior uveitis		1
Vitritis or vitreoretinitis	7	2
Chorioretinitis		2
Acute retinal necrosis		2
Panuveitis	3	2
Endophthalmitis	2	4

hyperalimentation, organ transplantation, cardiac surgery, diabetes mellitus, and treatment with high-dose systemic corticosteroids (40 to 120 mg/day) or cytotoxic agents (methotrexate or cyclophosphamide) (Table I). *Candida* infections were mainly present in patients who had had gastrointestinal surgery or hyperalimentation, whereas aspergillosis was noted mainly in organ transplant recipients, cardiac surgery patients, or individuals treated with immunosuppressive agents (Table III).

Of the 25 cases, 15 had the globes enucleated at surgery and the remaining 10 at autopsy. Of the 15 surgical cases, 11 revealed histopathologic features of *Candida* endophthalmitis and 4 showed features of *aspergillus* intraocular infection. Of the 11 globes with the morphologic features of *Candida* endophthalmitis, vitreous cultures were obtained in 6; growth of *Candida* was noted in all 6. In 5, the organisms were *Candida* albicans, and in 1, *Candida* tropicales. These 6 culture-positive globes, as well as the remaining 5 globes (in which cultures were not obtained), showed virtually identical histopathologic changes. These consisted of PAS-positive oval or round organisms with budding yeast forms, as well as pseudohyphae. These organisms stained well with GMS and Gridley stains (Fig 2). Alcian blue and mucicarmine did not stain the organisms. Vitreous cultures were obtained in 3 of the 4 cases with the morphologic features of aspergillosis. In 2, the cultures were positive for *Aspergillus*; the third was negative. Further speciation from 1 of the positive cases revealed *Aspergillus fumigatus*. The patient with the negative culture died from cerebral complications; autopsy revealed invasion of the middle cerebral vessel by septate branching hyphae. Cultures from this site grew *Aspergillus* species. Cultures were not obtained in the remaining case. Morphologically, all 4 cases revealed similar features, consisting of GMS-positive structures with distinct septae (Fig 3) and dichotomous branching with regular intervals at a 45° angle. There were no conidiophores. The fungal elements also stained positive with PAS. Gridley, alcian blue, and mucicarmine stains were not performed.

In 9 of the 10 cases in which eyes were obtained at autopsy, the eyes revealed the presence of mycotic organisms, morphologically consistent with *Aspergillus* as noted above. In 5 of the 10 cases, cultures were obtained prior to death; 4 had vitreous cultures and 1 had cultures of an embolus removed from a femoral artery. Of the 4 vitreous cultures, 1 was negative and 3 were positive for *Aspergillus*. Of these, further speciation of a case revealed A fumigatus. All 3 positive cases also revealed the growth of *Aspergillus* from the heart, lungs, and brain at autopsy. The femoral artery embolus grew *Aspergillus*. Autopsies of 3 other patients showed positive cultures for *Aspergillus* from heart, brain, or other organs (Table IB). In 1 of the 2 remaining autopsy cases, histologic examination of the left eye revealed *Candida* organisms in the vitreous, retina, subretinal space, and choroid, and cultures of the vitreous grew *Candida* albicans (Table IA). Cultures were not obtained in the remaining case.

Histopathologic examination of all 25 cases revealed the presence of an acute suppurative inflammation in the vitreous cavity. The inflammatory cell infiltration, however, was variable. Involvement of the retina and uvea was minimal in all but 1 of the eyes with *Candida* infection (case 12). In contrast, eyes with aspergillosis showed heavy infiltration of acute inflammatory cells in the retina, subretinal space, and choroid (Fig 4). Sections stained for fungi revealed differences in the distribution of fungal elements in eyes with *Candida* endophthalmitis compared to those with *Aspergillus* endophthalmitis. The former organisms were mainly localized to the vitreous abscess with the presence of few organisms in the retina. There were 2 cases that showed *Candida* in the vitreous as well as in the retina and choroid (Table IV).

Although mycelia of *aspergillus* were noted at the site of vitreous suppurative inflammation in all cases diagnosed as *Aspergillus* endophthalmitis, involvement of retina and choroid by these organisms was a prominent feature in 8

TABLE III: PREDISPOSING CONDITIONS IN THE DEVELOPMENT OF FUNGAL ENDOPHTHALMITIS.

FUNGI (NO. CASES)	ABDOMINAL SURGERY/ HYPERALIMENATION	ORGAN TRANSPLANTATION	CARDIAC SURGERY	TREATMENT WITH CORTICOSTEROIDS ± CYTOTOXIC AGENTS	DIABETES	ANTIBIOTICS	UNKNOWN
Candida (12)	6			1	3	1	1
Aspergillus (13)		4	4	4			1

TABLE IV: LOCALIZATION OF THE FUNGI IN 25 CASES OF ENDOGENOUS ENDOPHTHALMITIS

MYCOTIC AGENT NO. OF CASES	IRIS/CB NO. OF CASES	VITREOUS NO. OF CASES	VITREOUS AND RETINA NO. OF CASES	VITREOUS, RETINA SUBRETINAL SPACE AND CHOROID NO. OF CASES
Candida (12)	1	7	2	2
Aspergillus (13)	0	3	2	8

CB, ciliary body.

cases (Table IV). In all cases the organisms showed growth primarily within the subretinal space, with abundant organisms between the retinal pigment epithelium (RPE) and Bruch's membrane (Fig 5). The retinal and choroidal vessels (Fig 6) and the choriocapillaris showed the presence of organisms, but these fungal elements were most numerous between Bruch's membrane and the RPE. The latter was detached from Bruch's membrane by infiltration of mycelia (Fig 5). These organisms were also seen in the subretinal space or extending into the retina and choroid (Fig 7). However, they were more numerous in the sub-RPE and subretinal space than in the choroid. At the sites of heavy infiltration of the organisms, the choroid, RPE, and retina were necrotic. These sites also revealed the presence of numerous acute inflammatory cells. The mycelial structures stained well with PAS and GMS in the subretinal and sub-RPE sites despite the inflammatory cell infiltration (Fig 8). In contrast, in the choroid, these organisms were disintegrated and stained poorly with either PAS or GMS (Fig 9).

Distinct granulomatous inflammation was not observed in either *Candida* or *Aspergillus* endophthalmitis (Table V). However, foreign body multinucleated giant cells and several histiocytic cells were seen around the vitreous abscess. None of these giant cells contained fungal elements. The abscesses were multiple and relatively small in eyes with *Candida* infection (Fig 10), whereas the abscesses were large, with 1 or 2 filling the vitreous, in cases of aspergillosis.

Among the cases of intraocular aspergillosis, there were 6 that revealed mycelia in the walls of retinal and choroidal vessels (Fig 6). In the retina, these fungal elements appeared to extend from the luminal side and invade the surrounding extravascular retinal tissue and the vitreous (Fig 11). These cases also showed thrombosis of retinal vessels with focal areas of hemorrhages and exudates. Moreover, the retina was necrotic at these sites. Except for 1 case (case 12), such histologic changes were not observed in eyes with *Candida* infection.

TABLE V: TYPE OF INFLAMMATION IN 25 CASES OF ENDOGENOUS FUNGAL ENDOPHTHALMITIS

MYCOTIC AGENT	ACUTE SUPPURATIVE NO. OF CASES	COMBINED ACUTE & CHRONIC NO. OF CASES	PRESENCE OF GIANT CELLS NO. OF CASES
Candida (12)	11	1	4
Aspergillus (13)	12	1	5

Of the 10 autopsy cases, 9 patients died from disseminated mycotic infection. Autopsy findings were unavailable for 1 patient, but this patient was believed to have died from disseminated aspergillosis. Autopsies revealed disseminated aspergillosis in 8 cases and candidiasis in 1. Of the 8 cases of aspergillosis, 7 revealed cerebral vascular invasion by fungi (Fig 12). All of these cases showed cerebral infarction or hemorrhage in association with the infiltration of acute inflammatory cells in the brain or meninges. Six cases also revealed fungal endocarditis, and 3 showed the presence of septate, branching hyphae in the lungs, thyroid, and kidneys. One of the 8 cases of aspergillosis showed fungal endocarditis without cerebral mycosis. The lone case belonging to the *Candida* group revealed a large cerebral abscess containing organisms with features of *Candida*.

DISCUSSION

The present clinicopathologic study of endogenous mycotic endophthalmitis reveals differences in the clinical presentations and histopathologic features of *Candida* endophthalmitis and aspergillosis. These include systemic predisposing conditions, extent of retinal and choroidal involvement by the fungi, invasion of retinal and choroidal vessels by the organisms, variations in vitreous abscess formation, and mortality from central nervous system involvement. Gastrointestinal surgery and hyperalimentation were primarily noted in cases of *Candida* endophthalmitis; aspergillosis was seen mainly in individuals who received immunosuppressive agents or those who underwent organ transplants or valvular cardiac surgery. On the basis of such clear differences in predisposing conditions for the development of these 2 entities, it may be possible clinically to suspect *Candida* endophthalmitis in postoperative gastrointestinal surgery cases, whereas *aspergillus* infection would be expected in those with drug-induced immune suppression or in patients who have had cardiac surgery. Although individuals treated with high-dose systemic corticosteroids or cytotoxic agents such as methotrexate or cyclophosphamide are known to develop disseminated *Candida* or *Aspergillus* infection, diabetes seems to be a predisposing systemic condition for the development of *Candida* endophthalmitis, whereas leukopenia appears to be a predisposing condition for the occurrence of systemic aspergillosis.

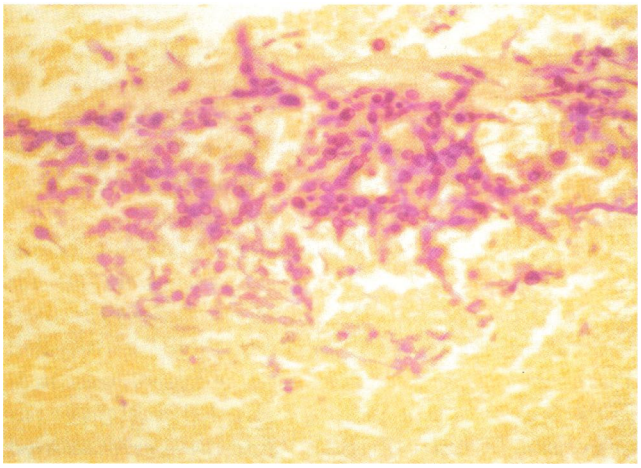


FIGURE 2
Gridley stain exhibits typical features of *Candida* (x300).

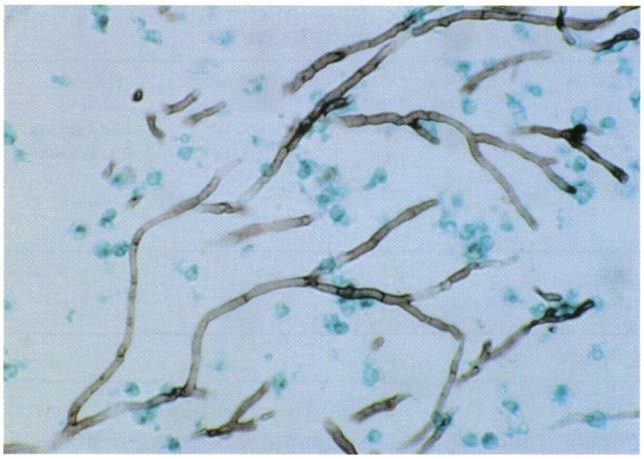
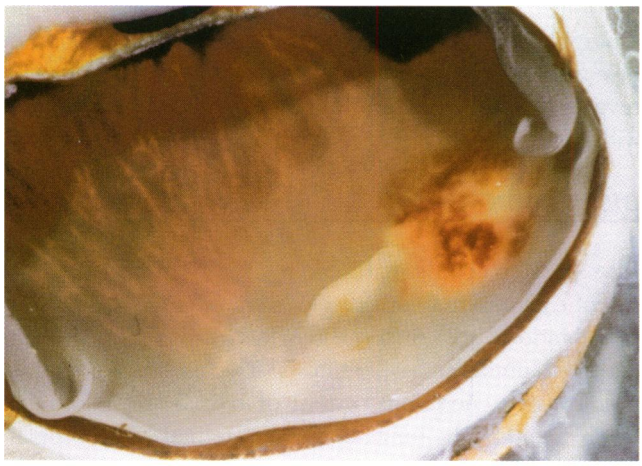


FIGURE 3
Note branching septate hyphae of *Aspergillus* (GMS, x240).



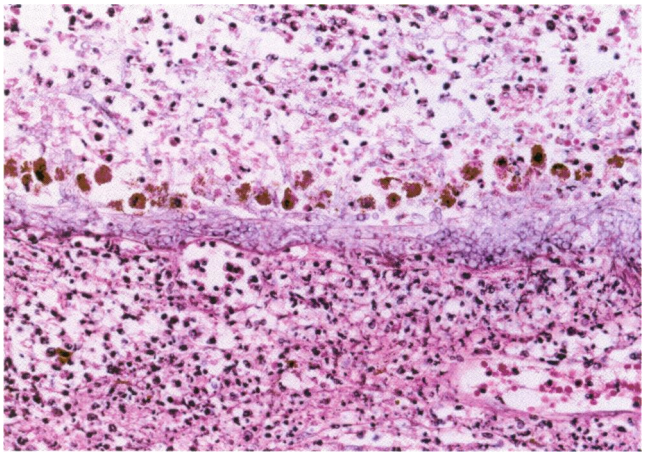


FIGURE 5
Distribution of fungi primarily between Bruch's membrane and retinal pigment epithelium. Inflammatory cells are present in choroid and subretinal space (PAS, x240).

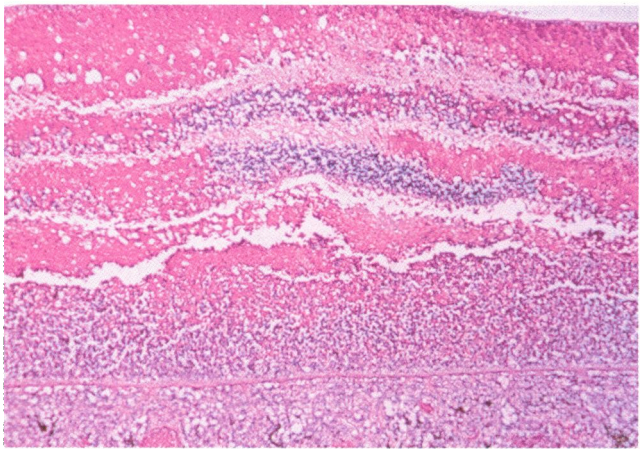


FIGURE 4
Top, Enucleated eye exhibiting chorioretinitis with hemorrhages. Bottom, Histologically, chorioretinal lesion reveals extensive hemorrhages in retina with infiltration of inflammatory cells in subretinal space and choroid (hematoxylin-eosin, x100).

The major underlying predisposing condition for the development of disseminated aspergillosis appears to be a prolonged granulocytopenia.[29-31] In the absence of granulocytopenia, factors such as chemotherapeutic agents or exposure to various antibiotics or corticosteroids were not associated with invasive aspergillosis, even in patients with leukemia. However, in leukemia patients, granulocytopenia persisting longer than 3 weeks was a major risk factor for the development of invasive pulmonary aspergillosis. Furthermore, recovery from neutropenia was generally associated with the elimination of such fungal infection.[30] Moreover, experimental animal studies revealed that disseminated aspergillosis was seen mainly in animals with granulocytopenia rather than in animals that were immunosuppressed with cyclosporine and methylprednisolone.[31]

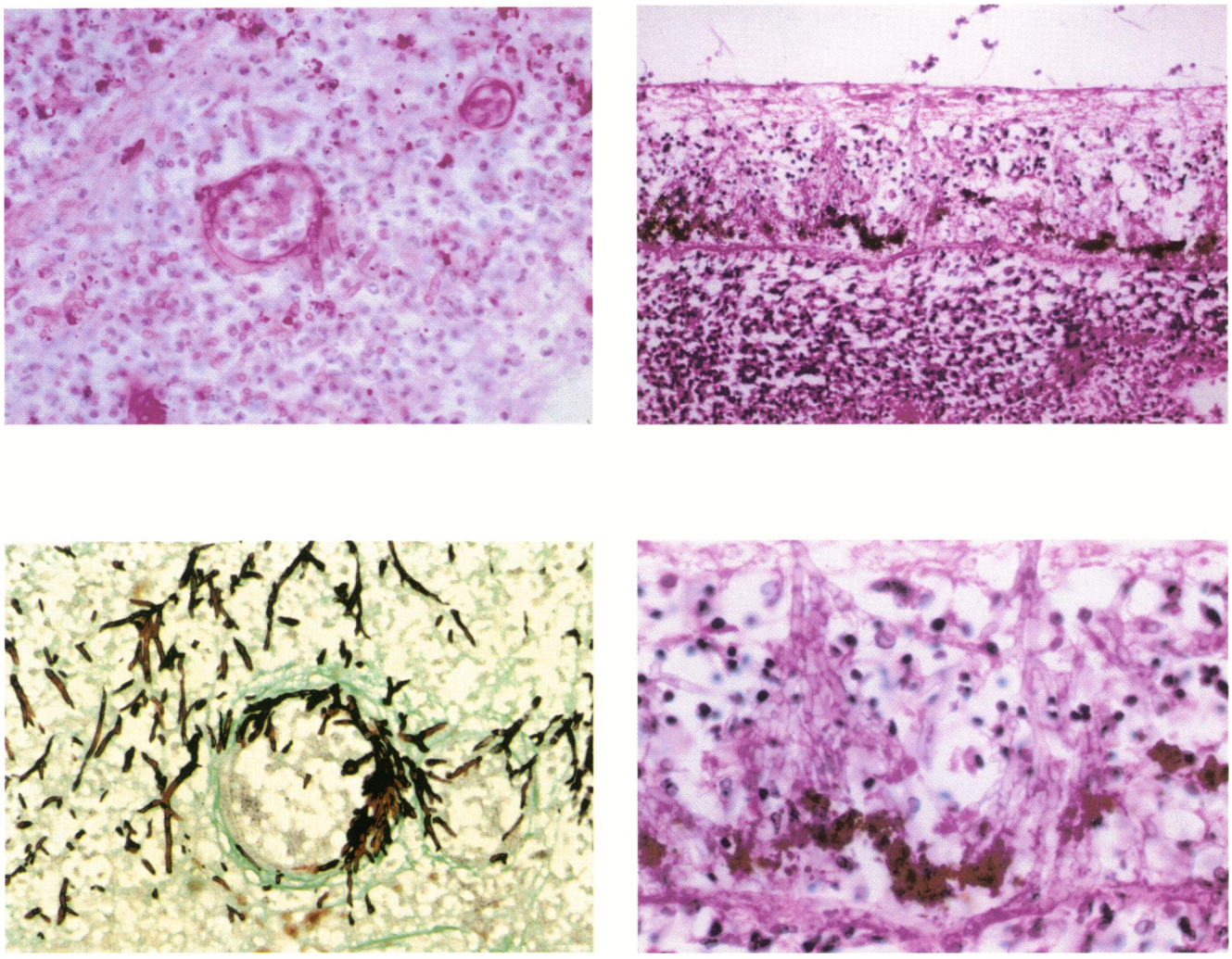


FIGURE 6

Top, Necrotizing retinitis shows invasion of retinal blood vessel by fungal elements (PAS, x300). Bottom, Choroidal vessel shows presence of fungal hyphae in vessel wall and adjacent choroidal tissue (GMS, x300).

Systemic candidiasis, including endogenous *Candida* endophthalmitis, is seen in individuals with diabetes mellitus or those treated with broad-spectrum antibiotics, or corticosteroids. Similarly, ileus associated with abdominal surgery may encourage the overgrowth of these organisms, with tissue invasion allowing access to the circulation.[32] In the present study, *Candida* endophthalmitis was seen mostly in patients who had undergone abdominal surgery or those with diabetes. In contrast, aspergillosis was noted in organ transplant recipients. The latter are typically treated with various cytotoxic agents to prevent rejection, and such treatment is known to be associated with granulocytopenia. Although our study shows the association of renal transplantation with the occurrence of *Aspergillus* endophthalmitis, Hunt and Glasgow[16] reported cases of *Aspergillus* endophthalmitis in individuals with orthotopic liver transplantation. Similarly, the endogenous

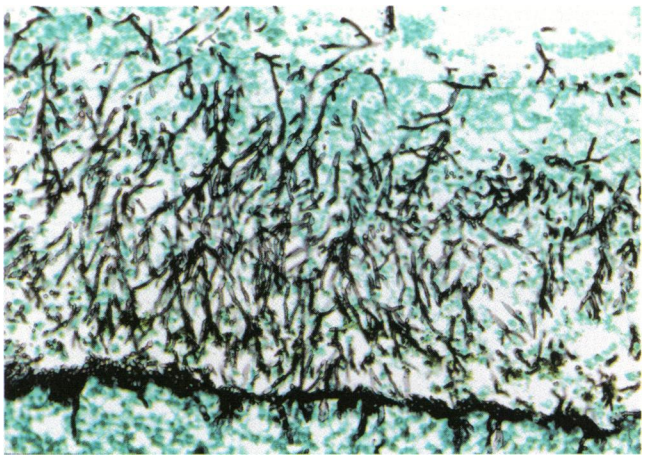


FIGURE 7

Top and Middle, Section of retina and choroid showing disrupted retinal pigment epithelium and extension of fungal elements into retina (hematoxylin-eosin, x120 and x360, respectively). Bottom, Fungal stain reveals distribution of fungi along Bruch's membrane and extension into retina (GMS, x225).

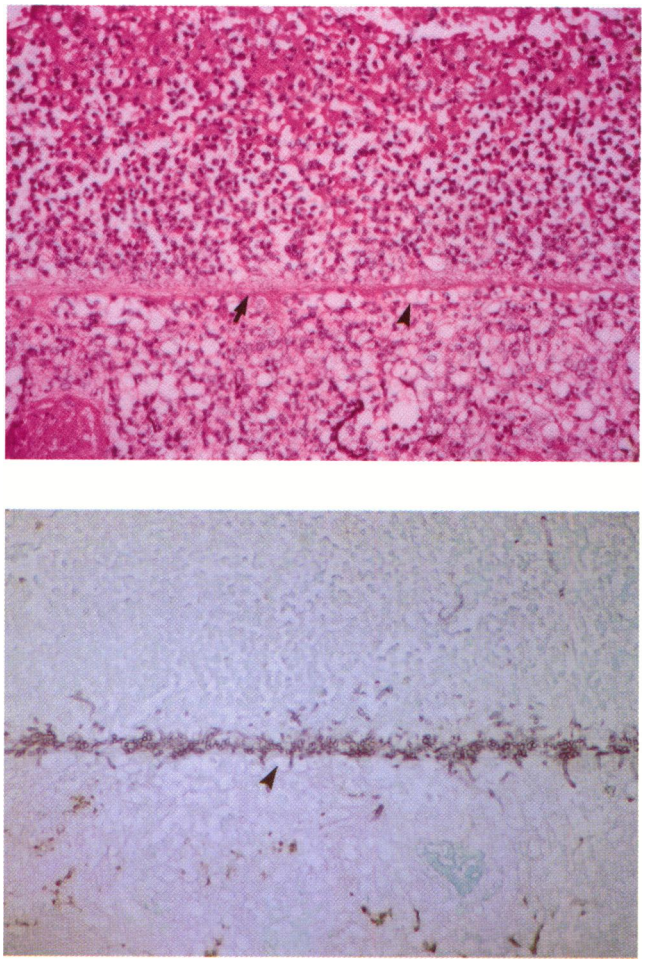


FIGURE 8
Top, Acute inflammatory cell infiltration is present in subretinal space (top) and choroid (bottom) (H&E x160; arrow indicates Bruch's membrane and arrow head pointing to choriocapillaris). Bottom, GMS-stained section (of region shown in Fig A) shows distribution of fungi along anterior surface of Bruch's membrane (GMS x160; arrow head pointing to choriocapillaris).

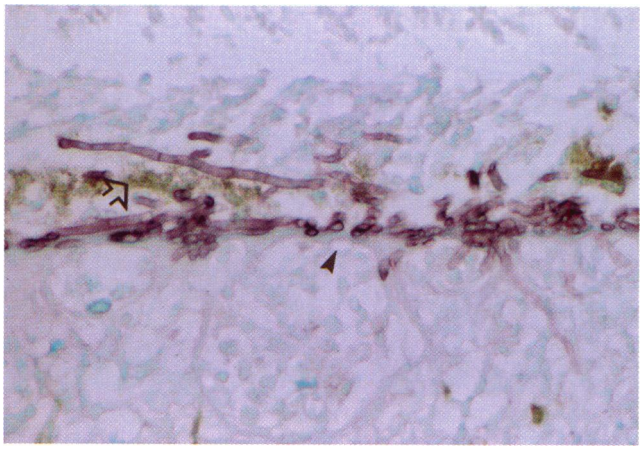


FIGURE 9
Note well-stained hyphae of Aspergillus in sub-RPE area and poorly stained hyphae in choroid (GMS x300; arrow and arrowhead pointing RPE and choriocapillaris).

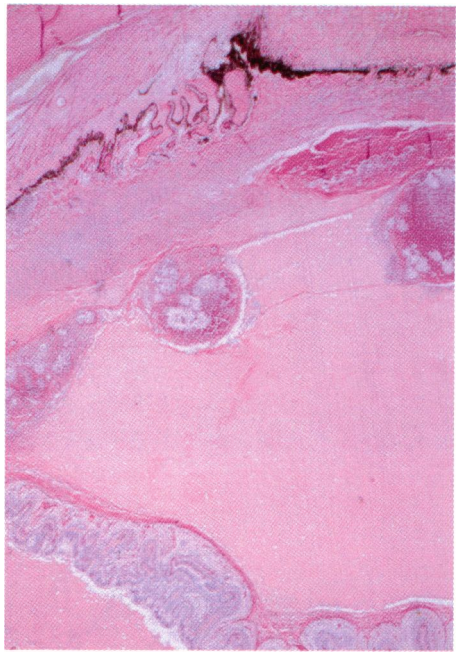
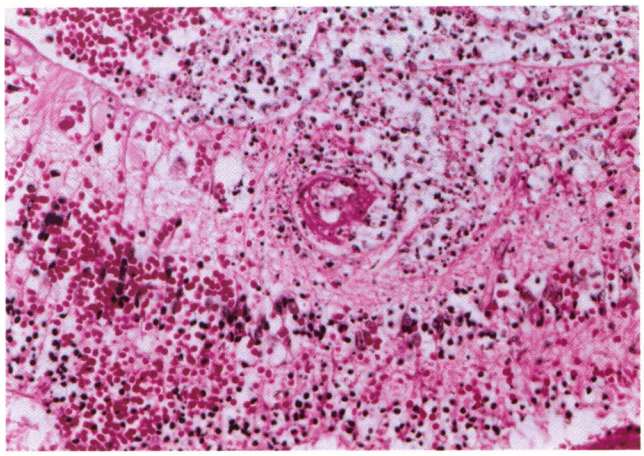


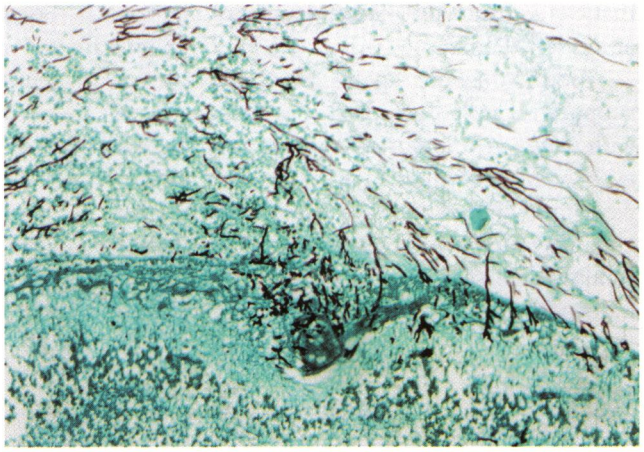
FIGURE 10
Multiple microabscesses in vitreous (H&E x15).

Aspergillus endophthalmitis has been reported to occur in cardiac and lung transplant patients.[9]

It is apparent that neutrophils are the most important line of defense against invasion of *Aspergillus* hyphae. These phagocytic cells can eliminate the hyphae by generating oxidants such as superoxide, hydrogen peroxide and related metabolites.[33,34] These oxidants can also damage *Candida* and other infectious agents. However, the occurrence of *Candida* endophthalmitis without granulocytopenia in postabdominal surgery patients or in individuals with diabetes suggests that the overgrowth of these organisms in the gastrointestinal tract or in diabetes (with increased availability of glucose, which is an important nutrient for *Candida*) may be important factors promoting the growth of these organisms.[1] It has been reported that glucose concentration is higher in the vitreous than in the blood of patients with insulin-dependent diabetes. Such increased levels in the vitreous appear to be due to the increased entry of glucose from plasma.[35,36] This increased concentration of glucose may play a role in the growth of *Candida*, particularly in patients with diabetes. The latter disorder is a well-recognized predisposing condition for development of endogenous *Candida* endophthalmitis.

Intraocular structures are endowed with abundant quantities of antioxidant enzymes. For example, the RPE is loaded with superoxide dismutase, catalase, glutathione peroxidase, and other antioxidant enzymes. Moreover, we have found that the RPE generates a protein, related to the transferrin family, known as retinal pigment epithelial





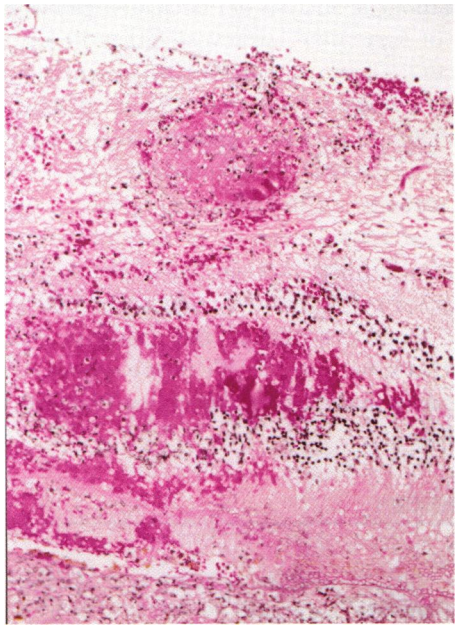
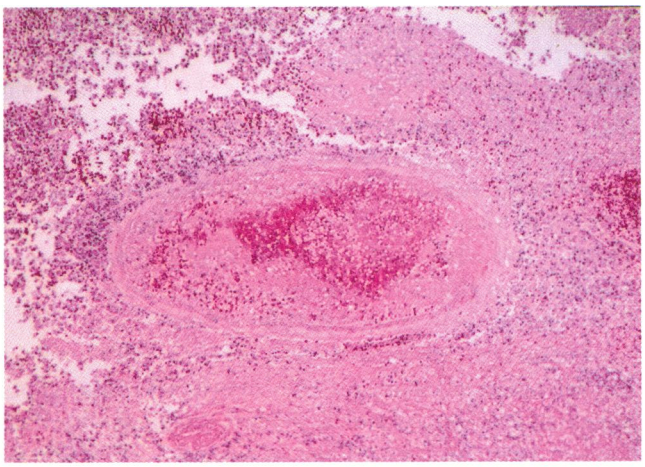


FIGURE 11

Top, Section of retina showing infiltration of acute inflammatory cells in retinal vessel and surrounding tissue. Note presence of erythrocytes in retina and inflammatory exudate (H&E x234). Middle, Adjacent section of retina reveals apparent extension of fungal elements from retinal vessel into vitreous (GMS x117). Bottom, Note thrombotic vessel, hemorrhages and exudates in retina (H&E x160).



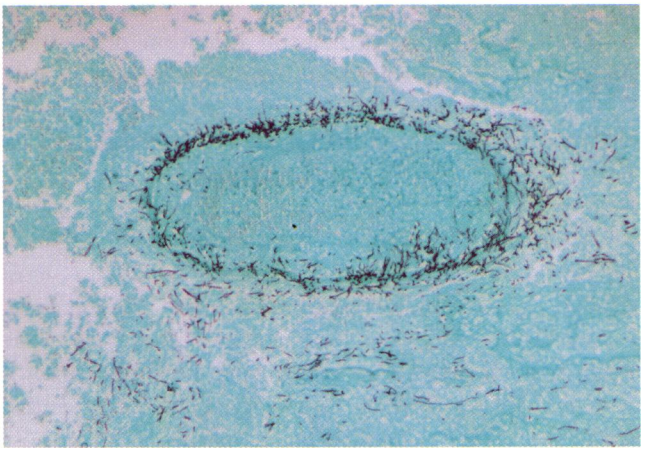


FIGURE 12

Top, Section of brain reveals thrombosis of cerebral vessel with inflammatory cell infiltration in adjacent tissue (H&E 100). Bottom, Cerebral vessel shows invasion of vessel wall by fungi (GMS x100).

protective protein (RPP).[37] This protein is unique in its ability to suppress superoxide generation by neutrophils.[37,38] The characteristic and overwhelming growth of *Aspergillus* mycelia in the subretinal and sub-RPE spaces (Figs 5, 7 through 9) suggests a role for RPE in enhancing the growth of these organisms.[37] It is possible that the distribution of antioxidant enzymes as well as the generation of RPP by RPE could prevent oxidatively mediated damage of the fungi despite the infiltration of neutrophils at these sites. Since the elimination of *Aspergillus* requires functioning neutrophils, while the growth of *Candida* requires nutrients such as glucose and a low pH, *Aspergillus* is most abundantly seen at the subretinal and sub-RPE region, whereas *Candida* is noted primarily in the vitreous. Therefore, vitreous biopsy or culture may yield negative results in some cases of intraocular *Aspergillus* infection.

Another important feature of aspergillosis was vascular invasion. Six of the 13 cases revealed fungal invasion of retinal vessels and growth along the choriocapillaries. This was not a feature in cases with *Candida* endophthalmitis.

Vascular invasion was associated with retinal necrosis and hemorrhages (Figs 6A and 11). In addition, foci of retina were invaded by fungi extending from the subretinal space. At these sites the retina was also necrotic and infiltrated by acute inflammatory cells. Such a finding indicates that the retinal necrosis can be either from vascular invasion or from direct tissue invasion by the fungal elements. Two cases with extensive retinal necrosis were misdiagnosed clinically as herpetic acute retinal necrosis. Both patients were treated initially with acyclovir.

Unlike the extensive retinal necrosis and choroidal damage noted histopathologically in eyes with *Aspergillus* infection, eyes with *Candida* showed small foci of retinal damage from invasion of the organisms. However, in *Candida* endophthalmitis, most of the inflammatory response was in the vitreous in the form of multiple microabscesses surrounding the organisms (Fig 10). These histopathologic findings provide an explanation for the relatively fair prognosis for eyes with *Candida* compared with the poor prognosis noted in *Aspergillus* endophthalmitis.

Although the diagnosis of *Aspergillus* endophthalmitis was made in some patients prior to their demise, most of the globes were obtained at autopsy. In contrast, *Candida*-infected globes were obtained at surgery. The present study, as well as several previous case reports, revealed that the death rate is high in patients presenting with *Aspergillus* endophthalmitis, particularly in those organ transplant recipients or cardiac surgery patients.[3,9,16,18,21] Autopsy findings revealed that the cause of death was cerebral involvement, with invasion of cerebral blood vessels (Fig 12) in particular. Even in patients with cardiac valvular aspergillosis, death was attributed to cerebral abscess and infarction from vascular invasion by the hyphae.

The initial clinical presentation of intraocular *Candida* infections differed from that of aspergillosis. The former presented primarily with signs of vitritis or of vitritis associated with retinitis. In contrast, features of acute retinal necrosis or chorioretinitis and endophthalmitis were observed in patients with aspergillosis (Table II). Such differences in clinical presentation appear to be due to preferential localization of the organisms in the vitreous in cases of *Candida* and to the presence of septate hyphae in retina and choroid in the eyes with aspergillosis. Although all of the specimens examined were enucleated eyes with marked damage to the vitreous and surrounding tissues, in the aspergillosis cases there was extensive retinal damage in the form of retinitis, retinal necrosis, and retinal and choroidal vascular invasion by fungal elements. These findings are consistent with the reported poor ocular prognosis in aspergillosis compared with *Candida* intraocular infections.

Despite the above differences between *Aspergillus* and *Candida* endophthalmitis, histologically both the infectious agents induced an acute suppurative inflammation. The organisms were surrounded mainly by neutrophils with sparse infiltration of histiocytic cells. The latter were seen admixed with foreign-body type multinucleated giant cells. These giant cells did not display infectious agents in their cytoplasm. There were few lymphocytes in the inflammatory infiltrate. These histologic changes indicate an acute fulminating inflammatory process without significant protection against the organisms by cell-mediated immunity. The latter is known to play an important role in the generation of various cytokines, such as TNF-α, interferon-γ , and interleukins, that can enhance the oxidative burst of neutrophils. Such an oxidative burst may play a role in eliminating fungi.

Both infectious agents were associated with acute suppurative inflammation in the vitreous cavity: In cases with *Candida*, the abscesses were multiple and small; in eyes with aspergillosis, in contrast, multiple abscesses were rarely noted and the abscesses were large. It is not clear why such a difference existed in the formation of vitreous abscesses even though both infectious agents induced suppurative inflammation.

CONCLUSION

Clinicopathologic analysis of enucleated globes harboring *Candida* or *Aspergillus* has revealed that there are distinct differences in the presentation of *Candida* intraocular infection compared with that of aspergillosis. Unlike *Candida* endophthalmitis, aspergillosis was seen in organ transplant recipients with granulocytopenia or in cardiac surgery patients. Clinically, aspergillosis presented as large foci of retinal necrosis or chorioretinitis and was associated with a high mortality rate. Although there is no substitute for culture-based diagnosis of fungal endophthalmitis, the above clinical and histologic observations indicate that it may be possible in some cases to differentiate *Candida* from *Aspergillus* endophthalmitis on clinical grounds.

REFERENCES

1. Pettit TH, Edwards JE Jr, Purdy EP, et al. Endogenous fungal endophthalmitis. In: Pepose JS, Holl GN, Wilhelmus KR, eds. *Ocular Infection and Immunity*. St Louis: Mosby; 1996:1262-1285.
2. McDonnell PJ, McDonnell JM, Brown RH, et al. Ocular involvement in patients with fungal infections. *Ophthalmology* 1985;92:706-709.
3. Jampol LM, Dyckman S, Maniates V, et al. Retinal and choroidal infarction from *Aspergillus*: Clinical diagnosis and clinicopathologic correlations. *Trans Am Ophthalmol Soc* 1988;86:422-440.

4. Lam DS, Koehler AP, Fan DS, et al. Endogenous fungal endophthalmitis caused by Paecilomyces variotti. *Eye* 1999;13:113-116.
5. Sheu SJ, Chen YC, Kuo NW, et al. Endogenous cryptococcal endophthalmitis. *Ophthalmology* 1998;105:377-381.
6. Scherer WJ, Lee K. Implications of early systemic therapy on the incidence of endogenous fungal endophthalmitis. *Ophthalmology* 1997;104:1593-1598.
7. Gabriele P, Hutchins RK. *Fusarium* endophthalmitis in an intravenous drug abuser. *Am J Ophthalmol* 1996;122:119-121.
8. Samiy N, D'Amico DJ. Endogenous fungal endophthalmitis. *Int Ophthalmol Clin* 1996;36:147-162.
9. Graham DA, Kinyoun JL, George DP. Endogenous *Aspergillus* endophthalmitis after lung transplantation. *Am J Ophthalmol* 1995;119:107-109.
10. Patel AS, Hemady RK, Rodrigues M, et al. Endogenous *Fusarium* endophthalmitis in a patient with acute lymphocytic leukemia. *Am J Ophthalmol* 1994;117:363-368.
11. Henderly DE, Liggett PE, Rao NA. Cryptococcal chorioretinitis and endophthalmitis. *Retina* 1987;7:75-79.
12 Essman TF, Flynn HW Jr, Smiddy WE, et al. Treatment outcomes in a 10-year study of endogenous fungal endophthalmitis. *Ophthalmic Surg Lasers* 1997;28:185-194.
13. Leen CL, Brettle RP. Fungal infections in drug users. *J Antimicrob Chemother* 1991;28(Suppl A):83-96.
14. Cogan DG. Immunosuppression and eye disease. First Vail Lecture. *Am J Ophthalmol* 1977;83:777-788.
15. Weishaar PD, Flynn HW Jr, Murray TG, et al. Endogenous *Aspergillus* endophthalmitis. Clinical features and treatment outcomes. *Ophthalmology* 1998;105:57-65.
16. Hunt KE, Glasgow BJ. *Aspergillus* endophthalmitis. An unrecognized endemic disease in orthotopic liver transplantation. *Ophthalmology* 1996;103:757-767.
17. Friedman AH, Chishti MI, Henkind P. Endogenous ocular aspergillosis. *Ophthalmologica* 1974;168:197-205.
18. Bodoia RD, Kinyoun JL, Qingli L, et al. *Aspergillus* necrotizing retinitis. A clinico-pathologic study and review. *Retina* 1989;9:226-231.
19. Rippon JW. Aspergillosis. In: Rippon JH, ed. *Medical Mycology: The Pathogenic Fungi and the Pathogenic Actinomycetes*. Philadelphia: WB Saunders; 1988:618-642.
20. Watts JC, Chandler FW. Aspergillosis, In: Connor DH, ed. *Pathology of Infectious Diseases*. Stamford, Conn: Appleton & Lange; 1997:933-940.
21. Boldrey EE. Bilateral endogenous *Aspergillus* endophthalmitis. *Retina* 1981;1:171-174.
22. Doft BH, Clarkson JG, Rebell G, et al. Endogenous *Aspergillus* endophthalmitis in drug abusers. *Arch Ophthalmol* 1980;98:859-862.
23. MacCormick WF, Schochet SS Jr, Weaver PR, et al. Disseminated aspergillosis. *Aspergillus* endophthalmitis, optic nerve infarction, and carotid artery thrombosis. *Arch Pathol* 1975;99:353-359.
24. Naidoff MA, Green WR. Endogenous *Aspergillus* endophthalmitis occurring after kidney transplant. *Am J Ophthalmol* 1975;79:502-509.
25. Vishniavsky N, Sagar KB, Markowitz SM. *Aspergillus* fumigatus endocarditis on a normal heart valve. *South Med J* 1983;76:506-508.
26. Michelson JB, Freedman SD, Boyden DG. *Aspergillus* endophthalmitis in a drug abuser. *Ann Ophthalmol* 1982;14:1051-1054.
27. Wilmarth SS, May DR, Roth AM, et al. *Aspergillus* endophthalmitis in an intravenous drug user. *Ann Ophthalmol* 1983;15:470-472, 474-476.
28. Demicco DD, Reichman RC, Violette EJ, et al. Disseminated aspergillosis presenting with endolphthalmitis. A case report and review of the literature. *Cancer* 1984;53:1995-2001.
29. Gerson SL, Talbot GH, Hurwitz S, et al. Prolonged granulocytopenia: The major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. *Ann Intern Med* 1984;100:345-351.
30. Todeschini G, Murari C, Bonesi R, et al. Invasive aspergillosis in neutropenic patients: Rapid neutrophil recovery is a risk factor for severe pulmonary complications. *Eur J Clin Invest* 1999;29:453-457.
31. Berenguer J, Allende MC, Lee JW, et al. Pathogenesis of pulmonary aspergillosis. Granulocytopenia versus cyclosporine and methylprednisolone-induced immunosuppression. *Am J Respir Crit Care Med* 1995;152:1079-1086.
32. Edwards JE Jr, Foos RY, Montgomerie JZ, et al. Ocular manifestations of *Candida* septicemia: review of seventy-six cases of hematogenous *Candida* endophthalmitis. *Medicine* (Baltimore) 1974;53:47-75.
33. Roilides E, Uhlig K, Venzon D, et al. Enhancement of oxidative response and damage caused by human neutrophils to *Aspergillus* fumigatus hyphae by granulocyte colony-stimulating factor and gamma interferon. *Infect Immun* 1993;61:1185-1193.
34. Washburn RG, Gallin JI, Bennett JE. Oxidative killing of *Aspergillus* fumigatus proceeds by parallel myeloperoxidase-dependent and independent pathways. *Infect Immun* 1987;55:2088-2092.
35. Lundquist O, Osterlin S. Glucose concentration in the vitreous of nondiabetic and diabetic human eyes. *Graefes Arch Clin Exp Ophthalmol* 1994;232(2):71-74.
36. DiMattio J, Zadunaisky JA, Altszuler N. Onset of changes in glucose transport across ocular barriers in streptozotocin-induced diabetes. *Invest Ophthalmol Vis Sci* 1984;25:820-826.
37. Rao NA, Wu GS. Free radical mediated photoreceptor damage in uveitis. *Prog Retin Eye Res* 2000;19:41-68.
38. Wu G-S, Rao NA. A novel retinal pigment epithelial protein suppresses neutrophil superoxide generation I. Characterization of the suppressive factor. *Exp Eye Res* 1996;63:713-725.

DISCUSSION

DR ALAN FRIEDMAN. Drs Rao and Hidayat have sought to elucidate a difference in the clinical or histopathologic appearance of *Aspergillus* sp. and *Candida* sp. endogenous endophthalmitis. They studied 25 enucleated (surgical or autopsy) eyes. Thirteen had endogenous *Aspergillus* endophthalmitis while 12 had endogenous Candida endophthalmitis. They concluded that *Candida* sp. were causative agents of endophthalmitis in patients with a history of gastrointestinal surgery, hyperalimentation or Diabetes Mellitus while Aspergillus sp. were causative agents in patients who had undergone organ transplantation or cardiac surgery. *Candida* sp. appeared to infect the vitreous primarily while Aspergillus sp. primarily affected the subretinal or subretinal pigment epithelial area with foci of retinal or choroidal vascular wall invasion. In addition there was a high rate of cerebral and cardiac infection in patients with *Aspergillus* endophthalmitis.

Since the early part of the 20th Century, isolated case reports of endogenous fungal endophthalmitis appeared in the literature. At first, sporadic cases were noted in otherwise healthy individuals. In the later part of the 20th Century, a trend developed in which patients were immune suppressed as a result of chemotherapy or in association with lymphoma/leukemia, metastatic carcinoma, following bone marrow, renal or liver transplantation,

severe burns, Diabetes Mellitus, hyperalimentation, intravenous drug abuse, chronically ill or debilitated and postoperative on antibiotics. AIDS patients seemed to account for rare cases. Though many fungi have been observed as causative agents of endogenous endophthalmitis, *Candida* sp. and *Aspergillus* sp. have been the leading culprits. Curiously though, unlike Drs Rao and Hidayat's experience with equal numbers, we found that *candida*-related infections were nearly 4 times more common than *aspergillus*-related cases.

As to the clinical and histopathologic appearance of endogenous fungal infections of the eye, it was common for *Aspergillus* sp. to produce a retinitis which rapidly evolved into an extensive endophthalmitis while *Candida* sp. were more likely to cause fluffy white-yellow non-discrete or discrete retinal lesions which spread into the vitreous producing one or more intravitreal abscesses. *Candida* sp. were sometimes associated with inflammatory precipitates along vessels in the uveal tract.

Is there a definite and definable pattern to various causative fungal agents that produce Endogenous endophthalmitis? Can one make an etiologic diagnosis on the basis of Clinical appearance? Rao and Hidayat give ample evidence that this may be so. However a few illustrations would seem to contradict their results leading one to conclude that a multicenter clinical trial would be in order. I would like to thank the authors for sending the manuscript in ample time for review prior to the meeting.

DR NARSING A. RAO. Thank you very much Dr Alan Friedman for your wonderful comments and for sharing your experience regarding the cases of *Candida* as well as the *Aspergillus*. The cases we reported here are in a way, mostly terminal, particularly those with *aspergillus*. Unlike your cases, the criteria for inclusion in our study were those who underwent enucleation, or, the eyes obtained at autopsy. Based on our cases, it appears that the *aspergillus* spreads from the chorio-capillaries into sub-RPE and subsequently, they invade the retina. Subsequent to the retinal involvement, the organisms extend into the vitreous cavity. Candida may also spread similiarly but most of the organisms reach the vitreous cavity and rarely do the enucleated globes show presence of *Candida* in the retina or in the choroid. Our study shows that there is preferential growth of *Aspergillus* along Bruch's membrane under the RPE whereas *Candida* are generally seen in the vitreous. Of course as you mentioned, future studies are required to test our hypothesis. But one takes into consideration, host factors like diabetes, corticosteroid treatment, GI surgery and granulocytopenia, the later seems to be the main predisposing factor for the *Aspergillosis* whereas the former conditions are seen in patients with *Candida* infection.