RETINAL AND CHOROIDAL INFARCTION FROM *ASPERGILLUS*: CLINICAL DIAGNOSIS AND CLINICOPATHOLOGIC CORRELATIONS*

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INTRODUCTION

Aspergillus species exists as a saprophytic fungus common in soil and decaying organic matter. The species is widespread in our environment and its spores are readily disseminated via air currents. It can normally be isolated from the skin and mucous membranes including the conjunctiva.

Aspergillus infections present in a variety of ways in susceptible humans. Inhalation of spores can cause bronchial asthma or allergic alveolitis. A frequent noninvasive or minimally invasive pulmonary colonization occurs following tissue damage from other diseases such as tuberculosis or bronchiectasis. A relatively indolent infection of the sinuses and orbits may be present. In the debilitated patient, however, *Aspergillus* invades and disseminates and may produce lesions in the lung, brain, kidney, gastrointestinal tract, myocardium, liver, spleen, and occasionally the eyes. *Aspergillus* endophthalmitis[1-23] may be seen in patients with disseminated aspergillosis, following penetrating ocular trauma or surgery, or in intravenous drug abusers.

This report presents three cases of endogenous aspergillosis with evidence of infarction of the retina. In all cases there was evidence of retinal vascular involvement clinically; choroidal whitening and exudative detachments suggested choroidal involvement in two cases (1 and 3). Histo-

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pathologically, there was evidence of choroidal vascular involvement (all cases) and retinal vascular involvement with inner retinal infarction in two cases (2 and 3).

CASE HISTORIES

CASE 1

A 63-year-old white man had a history of hypertension, degenerative joint disease, and myasthenia gravis. Acute myelogenous leukemia was diagnosed in February 1984. He was treated with induction chemotherapy consisting of daunomycin, ARA-C, and 6-thioguanine but his course was complicated by pancytopenia and fevers. He also received several antibiotics and amphotericin-B for possible bacterial and *Candida* sepsis and responded well. Ophthalmologic examination 1 month later revealed a visual acuity of 20/20 bilaterally with normal anterior segments. Retinal examination demonstrated a few exudates and hemorrhages felt to be consistent with leukemia and anemia. A repeat examination, 1 month later, showed resolution of the hemorrhages and a few persistent exudates. He was discharged from the hospital and was maintained in remission on weekly intravenous ARA-C injections.

In December of 1984 he was readmitted with sweats and fever. Physical examination again revealed normal visual acuity, ocular motility, pupillary responses, and "clear fundi." A chest x-ray showed a left lower lobe infiltrate with an effusion. A bone marrow aspirate revealed hypercellularity with 75% blast cells. The clinical impression was relapsed leukemia and pneumonia. Intravenous piperacillin and gentamicin were begun and ARA-C and AMSA were instituted.

The patient's hospital course was complicated by multiple fever spikes. He was treated with several additional antibiotics. Empirically amphotericin-B was begun in March of 1985 for possible fungal infection. During the 3 months of hospitalization, approximately 30 sets of blood cultures were drawn. Multiple sputum, urine, and cerebrospinal fluid (CSF) samples were cultured as well, but the only positive culture was one blood culture that grew *Staphylococcus epidermidis*, and diphtheroids.

In mid-March, he developed a new right upper lobe infiltrate. His antibiotics were adjusted to include vancomycin, gentamicin, erythromycin, and amphotericin-B, but he continued to spike high fevers. After 10 days the amphotericin-B was discontinued because of the possibility of a drug-induced fever. Twelve days later, he awoke with a complaint of loss of vision and severe pain in both eyes. Visual acuity was hand motions in each eye. The pupils were slightly reactive to light. Confrontation visual fields showed an homonymous defect on the left. The bulbar conjunctiva of each eye was marked chemotic with yellow fluid ballooning the conjunctiva over the lid. The anterior chamber appeared clear to a handlight examination. Ophthalmoscopic examination of the right eye revealed marked retinal whitening with infarction of the posterior pole which extended to the equator. A superior exudative retinal detachment was noted (Fig 1). All the retinal

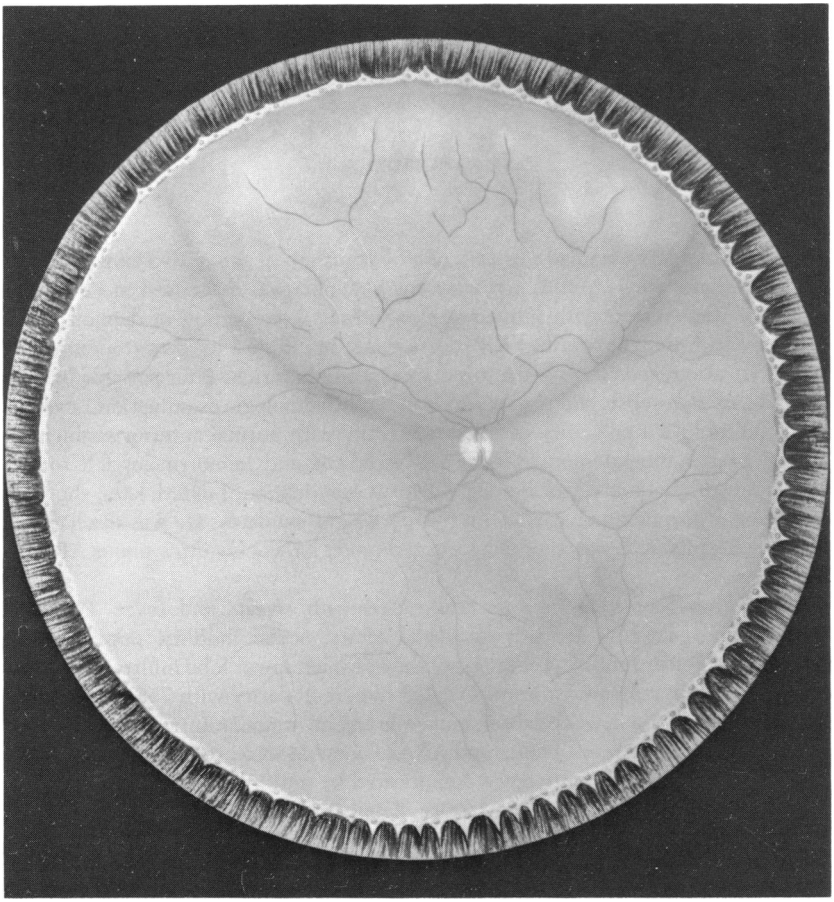

FIGURE 1
Clinical appearance, right eye, case 1 showing hazy media, superior exudative detachment, and retinal vascular occlusions.

arterioles appeared narrowed, and segmentation of retinal blood flow was seen in superior arterioles. The left retina was white (infarcted) with a bullous retinal detachment extending from the posterior pole to the equator. The clinical impression was massive retinal ischemic necrosis and exudative detachment from an infectious agent. Because of the occurrence of sudden retinal infarction, *Aspergillus* was thought to be the most likely organism with Phycomycosis a second possibility. The patient was thus restarted on amphotericin-B but died several days later.

An autopsy was performed 14 hours postmortem. Histopathologic examination revealed septate hyphae characteristic of *Aspergillus* with hemorrhagic infarcts and

abscess formation in the lungs, brain, thyroid, heart, and eyes (see below). A culture of the vitreous fluid obtained at autopsy grew *Aspergillus niger*. Death was attributed to disseminated aspergillosis with intracerebral hemorrhage from a ruptured mycotic aneurysm. The orbits appear normal except for edema. Both eyes were obtained for histopathologic examination.

OCULAR PATHOLOGY: CASE 1

Gross Examination

Both globes were opaque on transillumination and had similar internal findings. These included cloudy vitreous, posterior detachments of pale-appearing retinas associated with juxtapapillary hemorrhages, dense exudate in the subretinal and/or subretinal pigment epithelial spaces and thickened, mottled choroids beneath the retinal detachments.

Light Microscopy

Right Eye: Scatttered inflammatory cells occupied the anterior chamber and vitreous. The retina superiorly was detached from the equator to the optic nerve and the subretinal space filled with a cell dense sero-fibrinous exudate. Superiorly the retina, from the optic nerve to the equator, was distorted by full thickness necrosis and hemorrhaging with spread of erythrocytes and inflammatory cells into the adjacent vitreous. This corresponded to a heavy inflammatory cell infiltrate of the adjacent choroid. Elsewhere, the retina was detached but the rod and cone layers appeared intact. A few posteriorly located retinal vessels were occluded (Fig 2), but many more were surrounded by a dense periodic acid-Schiff (PAS) positive exudate (Fig 3). The Gomori methenamine silver (GMS) stain identified numerous branching, septate hyphal elements occluding the choriocapillaris and extending into the subretinal space. The retina and vitreous contained far fewer hyphae but occasional forms were present within seemingly patent retinal vascular lumens.

Left Eye: The retina and retinal pigment epithelium were detached from the optic nerve to the ora and the subretinal and subpigment epithelial space were filled with masses of inflammatory cells and proteinaceous exudate. Hemorrhage and necrosis distorted the retina posterior to the equator, and the adjacent retinal pigment epithelium was also necrotic. Although a few retinal vessels were possibly occluded many were highlighted by a dense PAS positive perivascular exudate. The rod and cone layer anterior to the equator appeared intact over uninvolved choroid. The posterior choroid was thickened by edema and inflammatory cells. Some mid-size choroidal vessels were obstructed (Fig 4). The GMS stain again demonstrated choriocapillaris occlusion by branching septate hyphae.

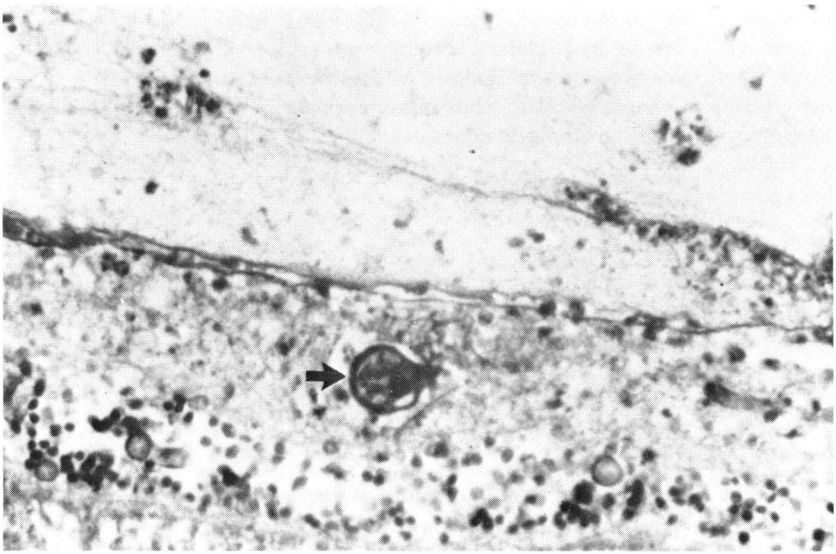

FIGURE 2
Case 1: Occluded retinal vessel is apparent (*arrow*) (PAS, × 200).

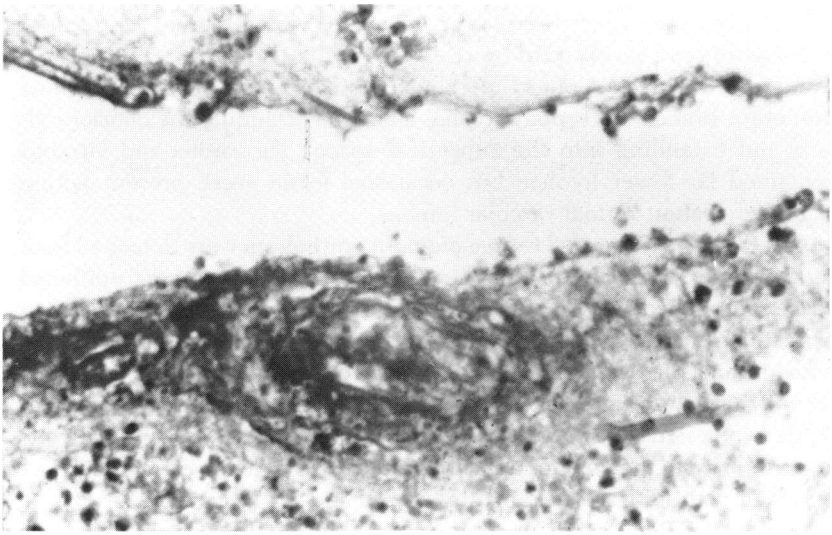

FIGURE 3
Case 1: Occluded retinal vessel with surrounding PAS positive exudate (PAS, × 400).

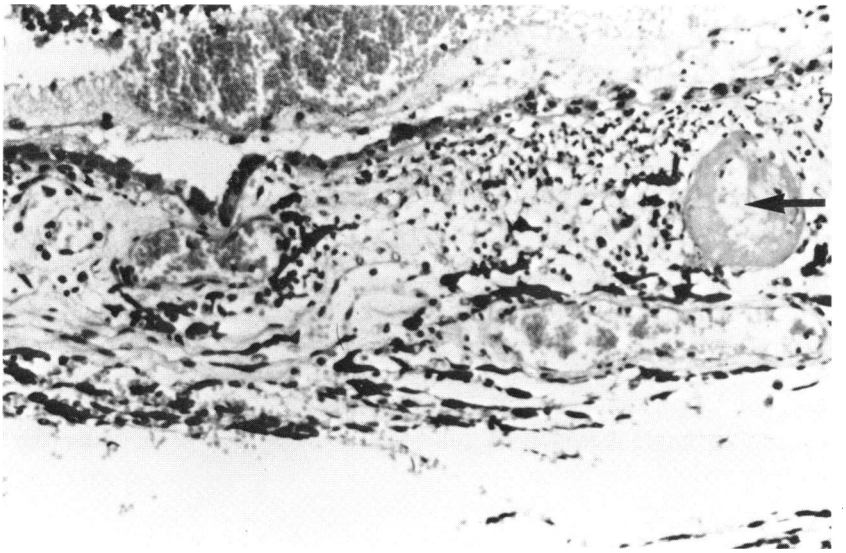

FIGURE 4
Case 1: Thrombosed choroidal vessel is seen (*arrow*). Inflammatory cells in choroid and subretinal hemorrhage are apparent (H&E, × 100).

Similar elements infiltrated the subretinal and subpigment epithelial space, retina and vitreous.

CASE 2

A 33-year-old white man complained of rapid loss of vision with pain and swelling of the left eye. There was no significant previous medical history. Initially the patient denied substance abuse, although he later admitted intravenous drug abuse.

On eye examination, visual acuity waas 20/20 in the right eye and 6/200 in the left eye. An afferent pupillary defect was present in the left eye. Moderate swelling of the left lids and marked conjunctival injection were present. One-eighth of the left anterior chamber was filled with an hypopyon. The fundus examination of the left eye showed a marked vitreous haze. In the posterior pole retinal vascular sheathing with intraretinal hemorrhages was noted. Inflammatory infiltrate was present throughout nasal retina. An obliterative retinal vasculitis was observed in the far temporal periphery with whitening of the retina. Examination of the right eye was normal. The tension was 16 mm Hg in each eye. HIV titers were negative. A tentative diagnosis of acute retinal necrosis syndrome was made and the patient was placed on intravenous acyclovir and systemic steroids.

Following treatment for 1 week, there was some clearing of the anterior chamber and the vitreous haze. The visual acuity improved to hand motions at 4 feet. Three weeks after initiation of therapy his condition worsened. The visual acuity was

reduced to light perception. There was increased anterior chamber reaction and vitreous haze, resulting in no visibility of the posterior pole. A left pars plana vitrectomy was performed, and vitreous cultures grew multiple colonies of *Aspergillus*. However, the eye became blind with increasing pain and enucleation was performed.

OCULAR PATHOLOGY: CASE 2

Gross Examination

The cornea was cloudy and the eye was opaque on transillumination. The anterior chamber was filled with blood and yellowish exudate. The lens was opaque. A multiloculated vitreous abscess, yellow-white in color, occupied the posterior part of the vitreous cavity, just anterior to the partially detached retina. The remainder of the vitreous space contained a serosanguinous fluid. A yellowish subretinal exudate was seen under the superior and inferior retina.

Light Microscopy

A fibrinous eosinophilic exudate, consisting of red blood cells, admixed inflammatory cells, and clusters of epithelioid cells filled the anterior chamber and chamber angle and extended into the posterior chamber. The superior chamber angle was open but the angle inferiorly was partially occluded by extension of a delicate fibrovascular membrane from the anterior iris surface.

Vitreal abscesses, consisting of central necrotic material surrounded by epithelioid cells and polymorphonuclear leukocytes, were noted. GMS stains revealed septate hyphae, 7 to 9 μ in diameter, with characteristic 45° dichotomous branching in the center of these abscesses (Fig 5). The retina was partially detached and intense perivascular sheathing with chronic inflammatory cells was seen. The superior quadrants of the retina were infiltrated with polymorphonuclear leukocytes but retained normal architecture. The retina in the posterior pole was largely necrotic with only limited areas of recognizable architecture. In the temporal periphery, inner retinal infarcts were noted, characterized by loss of the inner retinal layers including the nerve fiber, ganglion cell, and the inner plexiform layers and thinning of the inner nuclear layer (Fig 6). Massive gliosis and diffuse hemosiderosis were also present in these areas. Hyphae were identified in the retina (Fig 6, insert). In the inferior quadrants of the eye, focal choroidal ischemia was demonstrated by loss of outer retinal layers with focal occlusion of choriocapillaris but preservation of the retinal pigment epithelium. The nasal retina revealed evidence of both retinal and choroidal ischemia which corresponded to the clinically observed white

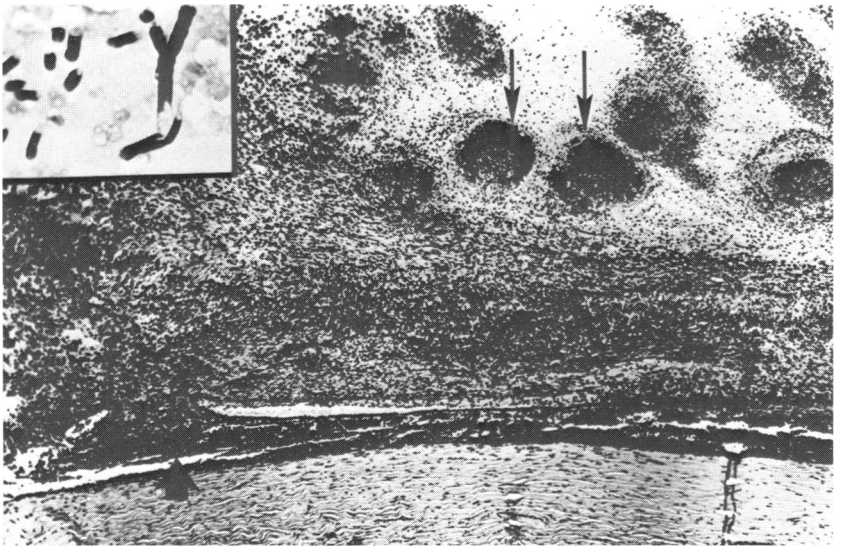

FIGURE 5
Case 2: Numerous vitreal abscesses (*arrows*). Retina and choroid are infiltrated with acute and chronic inflammatory cells. *Large arrow* shows chorioretinal infiltration extending to retina through RPE (GMS, × 100). Inset: In center of vitreal abscess, branching septate hyphae are seen (GMS, × 1000).

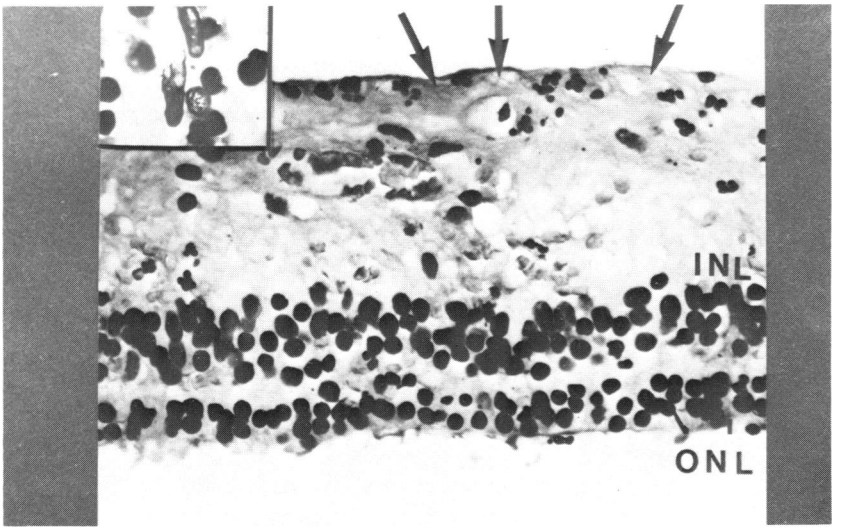

FIGURE 6
Case 2: Retinal infarcts. Inner ischemic retinal atrophy has resulted in loss of inner retinal layers (H&E, × 400). Inset: Hyphae in acutely inflammed retina (GMS, × 1000).

lesions (Fig 7). The subretinal space was filled with an eosinophilic exudate with red blood cells and polymorphonuclear leukocytes.

CASE 3

The clinical and histopathologic details of this case have been previously described in detail.[7] The patient was a 21-year-old woman with Goodpasture's disease, hypertension, hemoptysis, and renal failure. While on systemic prednisone and azathioprine, she developed the sudden onset of left eyelid edema, chemosis, and proptosis. Vision was no light perception in the left eye. There was left vitreous haze with a bullous retinal detachment, papilledema, occlusion of both the central retinal artery and vein, and hemorrhage in the infarcted retina. The patient died from aspergillosis. Light microscopy of the left eye showed necrotic retina with edema, hemorrhage, and fungal invasion. Fungal infiltration was seen in the central retinal artery and vein with occlusion (Figs 8 and 9).

The pigment epithelium was disrupted by hyphae lined along Bruch's membrane. Masses of hyphae invaded the choroidal vessels and the choroid was edematous, hemorrhagic, and necrotic (Fig 10). Hyphae were also present in the vitreous, the subretinal space and the optic nerve posterior to the lamina cribrosa.

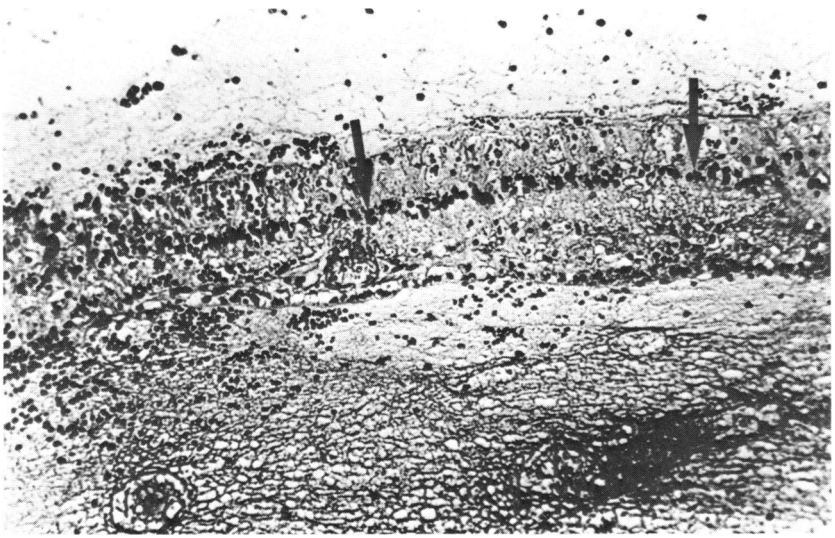

FIGURE 7

Case 2: Area with both retinal and choroidal ischemia with only a thin inner nuclear layer (*arrows*) remaining (H&E, × 160).

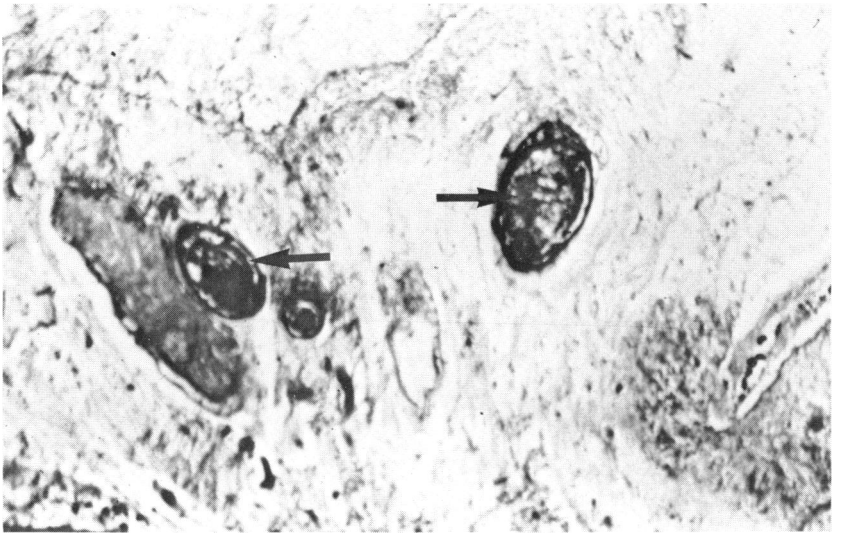

FIGURE 8
Case 3: Swollen optic nerve head is seen with occlusion of central retinal artery and vein (H&E, × 200).

FIGURE 9
Case 3: Fungi can be seen invading retinal vessel (GMS, × 400).

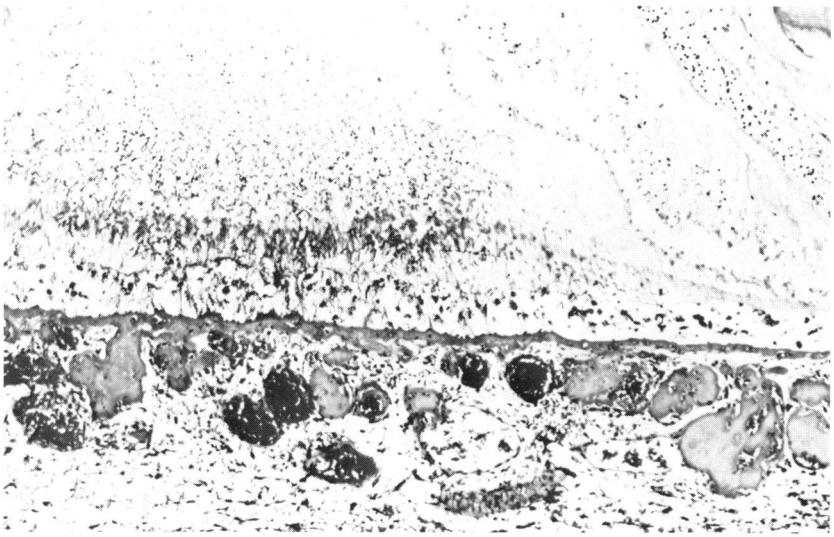

FIGURE 10
Case 3: Multiple occluded choroidal vessesl are apparent. Bullous detachment is seen with subretinal fungi (H&E, × 50).

DISCUSSION

Disseminated aspergillosis is often a difficult clinical diagnosis to confirm. Serologic tests are unreliable whereas blood cultures are usually negative [24] even in fulminant cases. Even in patients with pulmonary involvement, sputum cultures are rarely positive. Invasive culture techniques (eg, biopsies) are helpful, yet require a high index of suspicion. Vitreous biopsy with examination for hyphae and fungal cultures can be helpful when endophthalmitis is present.

The at-risk population for developing disseminated aspergillosis has been well defined. In one study,[24] 26 of the 34 patients had leukemia, 4 had lymphomas, 2 had other hematologic diseases, 1 had metastatic carcinoma, and 1 had collagen vascular disease. Disseminated aspergillosis with eye involvement has been reported in renal transplant recipients,[12] with congenital CMV infection,[13] and Goodpasture's syndrome.[7] Systemic corticosteroids, antibiotics, and cytotoxic immunosuppressive agents predispose individuals to invasive fungal disease. Endogenous *Aspergillus* endophthalmitis has been frequently reported as a localized eye disease in patients who abuse intravenous drugs, as seen in our case 2.[4,14,16-18,21] Exogenous *Aspergillus* endophthalmitis can occur following penetrating

ocular wounds or cataract surgery.[13,19,20,22]

Aspergillus has a predilection for invasion of blood vessels producing thrombosis, hemorrhage, infarction, and suppuration. Vascular involvement is the major cause of death. Hematogenous dissemination to the eye can occur following hyphal penetration of blood vessels. The histopathologic findings in our three cases provide insights into the mechanism of ocular damage. The retinas showed evidence of infarction involving the inner and outer retina as well as the retinal pigment epithelium. In all cases fungal elements were present in the choroid, retina, vitreous, and subretinal space. Hyphae were present in the choroidal vasculature of cases 1 and 3. This involvement was probably responsible for the exudative retinal detachments seen in these two patients. A few hyphae were seen in retinal vessels in case 1 and hyphae had produced occlusion of the central artery and vein in case 3. The eyes of case 2 showed temporal retinal ischemic patterns consistent with inner retinal infarction. This confirmed the clinically observed peripheral obliterative vasculitis with whitening of the retina. In this area invasion of the *Aspergillus* organism into the retina was demonstrated. Inferiorly in case 2 the eye exhibited choroidal ischemic patterns, characterized by loss of part of the inner nuclear layer, the outer plexiform layer, the outer nuclear layer, and the photoreceptor cell layer. Corresponding changes of the choroid included diffuse occlusion of the choriocapillaris with the retinal pigment epithelium relatively well preserved. The above changes would suggest *Aspergillus* invasion of the choroidal circulation, though we could not demonstrate hyphae in the choroidal vessels as seen in cases 1 and 3. The nasal retina in case 2 was damaged from retinal and choroidal ischemia, resulting in a thin inner nuclear layer with disappearance of all other layers of the retina.

When the retinal vasculature is acutely occluded there is infarction of the inner retinal layers. Inner ischemic atrophy of the retina demonstrates loss of all the inner layers, including the inner portion of the inner nuclear layer. On the other hand, the appearance of acute choroidal ischemic lesions differs depending upon size of the occluded arteries or arterioles.[25-29]

Ophthalmoscopically, lesions due to occlusion of large choroidal arteries produce triangular wedge-shaped infarcts, (previously reported with infection from phycomycosis[30]) while occlusion of small arteries produces geographic lesions; terminal precapillary choroidal arteriolar occlusions produce the so-called Elschnig's spot. Histopathologically, acute ischemic choroidopathy produces focal areas of infarction of the overlying pigment epithelium and outer retinal layers. At times, the pigment epithelium may survive but shows some atrophic changes with focal reactive proliferation.

In mild chronic ischemia of the choroid, collaterals may develop and the pigment epithelium, photoreceptor cells, and the outer plexiform layer may survive but the outer portion of the inner nuclear layer, which is normally nourished by the choroidal circulation, may disappear. Histopathologic studies of carotid artery occlusive disease[31] showed ischemic changes in both the inner (retinal) and outer (choroidal) circulations similar to case 2. The retina demonstrated almost total loss of the nerve fiber, ganglion cell, and inner plexiform layers, as well as reduction in the number of nuclei in the inner nuclear layer. In the periphery, focal areas of loss of the outer retinal layers with loss of pigment epithelium were associated with underlying sclerosis of the choriocapillaris. In the macular area, the pigment epithelium was relatively intact, but there was considerable reduction in the number of outer segments of cones and attenuation of the outer plexiform and nuclear layers. Another example of vascular occlusive disease affecting both the retinal and choroidal circulations is pulseless disease (Takayasu-Ohnishi's disease). Histopathologic studies[32,33] of this disease revealed retinal atrophy with a decreased number of ganglion cells and bipolar cells as well as a moderate reduction of the nuclei of photoreceptors, particularly at the posterior pole.

Many of the case reports of *Aspergillus* endophthalmitis do not give a clear description of the retinal findings. Some patients present as a marked vitreous haze, a white mass in the vitreous, or a white pupil. No retinal findings may be discerned in these patients. Some case reports do include retinal findings. Lederman and Madge[8] described focal chorioretinal lesions with vitreous haze. Naidoff and Green[12] and Walinder and Kock[15] noted multiple retinal hemorrhages while the latter authors reported development of a yellow-white vitreous mass later in the course of the disease. Demicco et al[3] described a central retinal artery occlusion early and later a heavy cellular infiltrate in the vitreous. Boldrey[1] described an eye which presented with a dense vitreous infiltrate. Examination during vitrectomy revealed necrotic retina with areas of vascular occlusion and hemorrhage. Later, the fellow eye became involved and showed arterial sheathing and occlusion, retinal necrosis, choroidal infiltrates, and punctate retinal hemorrhages. Sihota et al[23] described nonrhegmatogenous retinal detachment and retinal hemorrhages. Our three cases clinically showed evidence of retinal vascular sheathing, retinal hemorrhages, retinal vascular occlusion, and exudative retinal detachments. These findings were consistent with retinal and choroidal vascular invasion.

It seems logical to construct the course of ocular damage due to endogenous *Aspergillus* endophthalmitis as follows: hematogenous dissemination to the eye may produce retinal or choroidal vascular occlusion

either one or both of which may produce retinal necrosis; choroidal involvement produces retinal detachment. Vitreous inflammation represents spillover from the retinal or choroidal involvement. Nonvascular mechanisms may also damage the retina.

The differential diagnosis of *Aspergillus* endophthalmitis includes Phycomycosis—a disease caused by any of the three fungal groups *Rhizopus, Mucor,* or *Absidia*. These fungi colonize the nasal cavities and spread to the sinuses, orbits, and brain in debilitated patients, particularly those with diabetic acidosis. Immunosuppressed hosts with malignancies or previous treatment with corticosteroids, antibiotics, or cytotoxic agents are also suspectible. These fungi tend to invade blood vessels as does *Aspergillus*. The orbital findings may be similar to *Aspergillus* infection but intraocular involvement is rare with Phycomycosis.

Treatment of *Aspergillus* endophthalmitis includes intravitreal injection of amphotericin-B, and/or systemic amphotericin-B, and in some cases vitrectomy. Early diagnosis is essential; only a few of the many reported cases[1-23] regained useful vision, often due to delayed diagnosis. In drug abusers who do not reveal their substance abuse, *Aspergillus* infection may not be considered and corticosteroid therapy may be initiated when it is actually contraindicated.

Disseminated aspergillosis is becoming more common with the widespread use of corticosteroids, antibiotics, and cytotoxic agents. The incidence of *Aspergillus* endophthalmitis in disseminated aspergillosis is unknown.[3] In some cases, endophthalmitis is the presenting complaint in endogenous aspergillosis is seen in cases 2 and 3. In drug abusers, eye involvement may be seen without other evidence of infection. Early recognition of intraocular aspergillosis may hasten diagnosis and improve prognosis. Awareness of *Aspergillus'* propensity to cause retinal and choroidal infarction may improve the ophthalmologist's ability to diagnose this vision- and life-threatening event.

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DISCUSSION

DR JOHN D. BULLOCK. I appreciate the opportunity to discuss the paper by Doctor Jampol and associates, concerning disseminated *Aspergillus* infections to the eye. The authors describe three patients who developed disseminated endophthalmitis presumably from *Aspergillus*. The diagnosis of aspergillosis in the authors' first case was undeniable, since a postmortem culture of the vitreous fluid grew *Aspergillus niger*. In the second patient, vitreous fluid removed during a pars plana vitrectomy grew multiple colonies of *Aspergillus*. Speciation was not reported. The diagnosis of aspergillosis in the authors' case 3 was made on the basis of a tissue appearance of "fungal hyphae showing branching at 45 degrees. . . ." This description is considered inconclusive by microbiologists in diagnosing aspergillosis, because of the similarity of other organisms, especially the Zygomycetes and *Pseudallescheria boydii*.

Pseudallescheria boydii is an opportunistic fungus which masquerades as *Aspergillus*. This common soil organism is morphologically indistinguishable from *Aspergillus* in tissue section and has the identical pathologic tissue reactions of suppuration and vascular invasion with infarction, hemorrhage, ischemia, and necrosis. The systemic features include pulmonary infection with hemoptysis and frequent extrapulmonary dissemination. In addition, *Pseudallescheria boydii* has been reported to cause endophthalmitis, orbital cellulitis, and corneal ulceration, and is, thus, important to the ophthalmologist. It is crucial to make the differentiation between these two organisms since amphotericin-B, the favored treatment of *Aspergillus*, usually has no effect on *Pseudallescheria boydii*, while miconazole and ketoconazole both have potential for the treatment of pseudallescheriasis. Thus, to make a definitive diagnosis of aspergillosis, the organism must be cultured, and, ideally, speciated.

Doctor Jampol and co-workers report vascular invasion by *Aspergillus* with infarction of the retina and choroid, both clinically and histopathologically. The text of their article describes clinical and histopathological features which might be consistent with their thesis that the ophthalmic features of *Aspergillus* endophthalmitis are caused by retinal and choroidal vascular infarction from invasion by *Aspergillus* organisms. Their only documentation of all of the described clinical features, however, is a single choroidal drawing of one eye of the patient in case 1. The text describes histopathologic features which include numerous Gomori-methenamine silver positive branching septate hyphal elements in the vitreous and retina and occluding the choriocapillaris, mid-sized choroidal vessels, and central retinal artery and vein. These described histopathological features, however, were not readily seen in six of the seven photomicrographs provided to the discussant. Thrombosed vessels are shown but they are occluded by fibrin thrombi. Fig 2 shows a questionable hyphal element in an occluded questionable retinal vessel. The legend for Fig 8 states "fungi in thrombosed vessel." The photomicrograph does show fungi and an occluded vessel, but most of the fungi are outside of the vessel. Fig 8, however, relates to the patient in case 3, and must be eliminated due to absence of a culture.

In addition, the authors emphasize that vaso-occlusive chorioretinal disease should suggest *Aspergillus* infection to the ophthalmologist. Disseminated intravascular coagulopathy (DIC) can be associated with any form of septicemia or widespread infection, and it can also cause profound ocular changes with choroidal vascular occlusion and frequently associated secondary retinal detachment. Thus, DIC also should be included in the differential diagnosis of ocular aspergillosis.

The authors state that patients with disseminated ocular aspergillosis can present as a vitritis with focal chorioretinal lesions. This identical clinical picture, however, can be seen with other infectious agents, such as *Nocardia asteroides*. In addition, metastatic endophthalmitis in immunocompromised patients has been reported in association with a large variety of other organisms. Thus, it is unreliable to make a diagnosis of a specific microorganism on the basis of the described clinical findings. Therefore, vitrectomy with culture, and cultures elsewhere, must be done to establish a definite diagnosis.

The authors' therapeutic recommendations are given as follows: "treatment of *Aspergillus* endophthalmitis includes intravitreal injection of amphotericin-B, and/or systemic amphotericin-B, and, in some cases, vitrectomy." Green et al found poor ocular penetration of amphotericin-B when given intravenously. Naidoff and Green stated "no case of *Aspergillus* endophthalmitis has been sucessfully treated with amphotericin-B therapy administered intravenously." Lance and co-workers recommend ". . . complete vitrectomy, accompanied by intravitreal and intravenous amphotericin-B." I would concur with this final recommendation.

I have enjoyed reviewing this paper and sharing my thoughts and experiences on this previously rare but increasingly important problem. I thank the authors for sending their manuscript in sufficient time for me to prepare my discussion.

DR J. DONALD M. GASS. I want to call attention to another infectious disease that can cause this syndrome of prominent vascular occlusion of both the retina and choroidal circulations. It is herpe zoster, which is at least one of the major causes of acute retinal necrosis syndrome (ARN). In some of these cases the most striking clinical finding when they first present is that of retinal arterial occlusion. As a matter of fact, two patients with ARN in which herpes zoster was eventually identified in Miami were misdiagnosed on initial presentation as central retinal artery occlusion occurring as part of the ischemic ocular syndrome caused by carotid artery obstruction. They were transferred to the neurology service. Their evaluation was negative and by the time they were sent back to the Eye Institute, the fundus picture had progressed to that of ARN. Thus ARN caused by herpes zoster and perhaps herpes simplex must be considered in patients presenting with evidence of retinal artery obstruction, when it is accompanied by vitreous inflammation.

DR DAN B. JONES. I would like to commend Doctor Jampol for compiling these cases and recognizing endogenous ocular infection by *Aspergillus* in his first case. Unlike endogenous *Candida* endophthalmitis and other disseminated infections with ocular involvement, it is extremely difficult to diagnose aspergillosis by

indirect methodology. I am unaware of the organism being recovered from blood in disseminated infection and serological testing and methods for detection of antigen in blood and other materials are simply not reliable. The presence of multifocal hemorrhages in his cases is also of interest as others have emphasized that this may be a helpful sign in distinguishing the entity from *Candida* retinitis. Our experience would tend to go along with this although the presence of intraretinal hemorrhages with this type of infiltrate is certainly not a reliable feature.

The apparent predilection of this organism for the retina and choroid as opposed to the tendency for *Candida* to invade the vitreous is most intriguing, and I wonder how we can answer this question on the variance in pathogenesis. I would also be interested to know if there was evidence of other organ involvement in these three cases which may provide some additional idea on the severity of infection and support the proposed mechanisms of vascular occlusion.

Dr David Knox. My first experience with this disease was with a young man who denied recent use of intravenous drugs. He claimed 6 weeks since the last time he used street drugs and he had aspergillosis. These patients lie. You ask them straight out, have you used drugs, and many of them will say, no. You will have to be always worried about that. In retinal vasculitis I would encourage all of you to think about the intestinal parasite *Giardia lamblia*. We have had a recent patient with a retinal vasculitis with what looked like retinal necrosis syndrome and was loaded with Giardia. That is something to include in the differential.

Dr Lee M. Jampol. I thank the discussants for their comments about my paper. I would like to answer some of the questions that were raised. Doctor Bullock, I assume you don't think there is any doubt about the diagnosis of *Aspergillus* in the first two cases. In case 3, which was seen in the early 1970s, the autopsy diagnosis was disseminated aspergillosis. I thank you for bringing to our attention this rare organism that can resemble *Aspergillus*. In terms of your suggestion that disseminated intravascular coagulopathy looks similar to *Aspergillus*, I disagree. Usually DIC is seen in premorbid patients. The clinical findings rarely involve the retinal and choroidal circulations simultaneously. One can see findings in the retina (eg, retinal hemorrhages); one can see nonrhegmatogenous detachments of the retina because of choroidal involvement. In my experience DIC does not resemble the inflammatory picture with retinal and choroidal ischemia that we saw in our patients.

The ophthalmologist should not just stand back and say the patient has "an opportunistic infection." *Nocardia* looks very different from *Aspergillus*. It is a choroidal abscess that has a very characteristic appearance. *Candida* also looks very different. It is usually a fluffy, white preretinal exudate which extends into the vitreous. CMV also has a characteristic appearance. We can look in these eyes and make a strong guess—we're not always right—what the organism is and I think we should do just that. This helps to suggest the appropriate tests. It has been pointed out blood cultures for *Aspergillus* are almost useless. So unless you suspect *Aspergillus* you are probably going to miss the diagnosis.

Doctor Gass reminds us that herpes zoster is also a cause of vascular occlusion and uveitis. Doctor Jones, I don't know why this organism involves blood vessels as does *Phycomycosis*. This is an interesting question. The eye is not the only organ in which this occurs. Many of these patients have infarctions throughout the body and there was a discussion in the *New England Journal of Medicine* not too long ago emphasizing this point (*N Engl J Med* 1987; 317:1151-1152).