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Preventing reactivation of ocular histoplasmosis: Guidance for patients at risk

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Abstract

BACKGROUND: Ocular histoplasmosis syndrome (OHS), a significant cause of vision loss in young and middle-aged adults, is associated with the fungus *Histoplasma capsulatum* (Hc). There is considerable evidence that recurrent reactivation of perimacular ocular histoplasmosis lesions is an important cause of disease progression and that vision loss is at least, in part, a consequence of host sensitivity to fungal antigen.

METHODS: The etiology and pathogenesis of OHS is reviewed and specific recommendations are made for patients with OHS that may decrease the risk of reactivation of ocular histoplasmosis lesions and slow disease progression.

CONCLUSION: Patients with perimacular chorioretinal scars secondary to OHS should be informed by the clinician that they are at risk for vision loss; they should be told the symptoms of choroidal neovascularization and how to self-monitor their vision with an Amsler grid. We recommend they also be instructed on how to decrease their risk of reinfection by Hc. Aggressive treatment of dermatomycoses, onychomycosis, vaginal candidiasis, and other chronic fungal infections may decrease the risk of reactivation of ocular lesions. Patients with OHS who are considering LASIK surgery should be informed that the procedure may trigger choroidal neovascularization.

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Histoplasmosis is one of the most common respiratory mycoses, infecting an estimated 200,000 to 500,000 individuals annually in regions of the midwestern and southeastern United States where it is endemic.[1] The ocular histoplasmosis syndrome (OHS) describes a classic triad of ocular findings comprising atrophic chorioretinal scars, peripapillary scarring, and a disciform macular scar. It is not associated with anterior segment inflammation nor with inflammatory cells in the vitreous. Because Koch's postulates have not yet been met—no organism has been recovered from a lesion and then cultured and recovered in an animal model—the association with *Histoplasma capsulatum* (Hc), a dimorphic, facultative, intracellular pathogen of mammalian macrophages, remains unproven. There is, however, substantial epidemiologic and laboratory evidence linking the disease with the organism. Nonetheless, the condition is often referred to as *presumed* ocular histoplasmosis syndrome.

Disciform macular scarring associated with OHS leads to a loss of central vision in the affected eye. A scar will develop after the resolution of a hemorrhagic or serous detachment that is usually associated with choroidal neovascularization. There is evidence to suggest that the disciform process usually arises in areas of the fundus afflicted by a preexisting atrophic scar.[2,3] Treatment measures usually are directed toward minimizing the size of the resulting scar and thereby minimizing the size of the scotoma. Cur-

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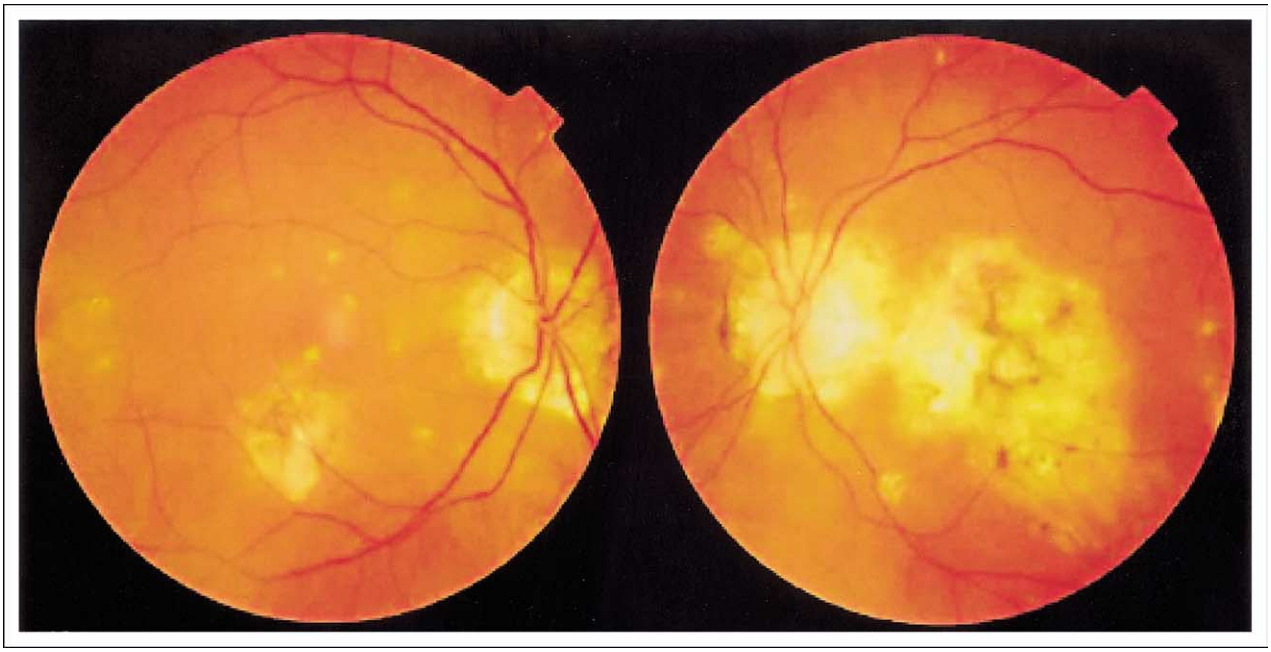

Figure 1 Fundus photographs show characteristic features of OHS. Numerous atrophic scars and peripapillary scarring are seen in each eye. A larger chorioretinal scar is seen inferior to the fovea in the right eye, suggestive of prior reactivation in this region. The macula of the left eye has been destroyed by a large disciform lesion. The visual acuity was 20/20 O.D. and 20/400 O.S.

rent treatments include photocoagulation, photodynamic therapy, antiangiogenic agents, steroids, surgical excision of the choroidal neovascular membrane, and macular translocation.

There are no proven effective measures that will prevent or delay the onset of disciform disease associated with OHS. However, epidemiologic and laboratory research points toward measures that may minimize the risk of maculopathy. This report explores that evidence and presents advice for patients at risk.

The ocular histoplasmosis syndrome

Atrophic scars

The cornerstone of ocular histoplasmosis is an atrophic chorioretinal scar with a characteristic "punched out" appearance known as a "histo spot." These scars tend to aggregate around the optic disc to produce a halo of peripapillary scarring. An atrophic scar in the perimacular or peripapillary region may trigger choroidal neovascularization and disciform scarring of the macula (*see* Figure 1).

The atrophic chorioretinal scars of OHS are yellowish white in color with a minimal amount of pigment. Size is typically 0.1 to 0.2 disc diameters. They are bilateral in 50% to 60% of cases. Patients may have no lesions at all or up to as many as 100 lesions per eye. The number of scars is fairly constant across all age groups, a finding that supports the theory that the scars develop early in life, probably at the time of initial exposure to Hc. They may occur anywhere in the fundus, but most are located posterior to the equator. They are distributed randomly throughout the midperiphery and posterior fundus, although about 5% of patients will have linear chains of spots called streak lesions arranged circumferentially in the equatorial region of the fundus.[4] It is well established that new scars can develop in locations that were previously normal by both clinical examination and fluorescein angiography.[5] Scars can enlarge and change color, and others may fade or disappear. The cause of these changes is unknown, but it has been hypothesized that a chronic smoldering inflammation may be responsible.[6]

Peripapillary scarring is seen in about 20% to 30% of patients with OHS and appears to represent a coalescence of histo spots around the optic disc. The reason for the affinity of the scars for the peripapillary region is unknown. Choroidal neovascularization can arise from peripapillary scarring. A greater degree of peripapillary scarring is not associated with higher risk for peripapillary choroidal neovascularization.[5]

Maculopathy

Ocular histoplasmosis usually remains asymptomatic until the development of macular disease. It is estimated that a disciform lesion will develop in 5% of patients with OHS.[5,7] The patient with a disciform lesion will present clinically with symptoms typical of exudative maculopathy, including blurred vision, metamorphopsia, and a positive scotoma. Examination will usually find signs of choroidal neovascularization, including serous or hemorrhagic detachment of the sensory retina. It is believed that most, if not all, disciform lesions arise from pre-existing atrophic chori-

oretinal scars.[2,3] It has been estimated that patients with perimacular atrophic scars have a 10-fold higher risk of disciform lesions developing compared with individuals who do not have perimacular scars.[8] Hawkins and Ganley[9] reported that no disciform lesions developed in eyes that contained peripheral atrophic scars over a 15-year period.

The visual prognosis for patients with disciform maculopathy associated with OHS is poor. Approximately 20% of patients with untreated lesions will retain a final visual acuity of 20/40 or better, whereas 70% will have a final visual acuity of 20/200 or worse.[10] Atypical cases of histoplasmic maculopathy may present without neovascular membranes. Instead, these patients will present with active inflammatory chorioretinal lesions in the macular region. Such lesions usually resolve without the development of choroidal neovascularization or loss of visual acuity.[11]

The peak incidence for the onset of choroidal neovascularization is between the ages of 30 and 45 years.[5,12] Interestingly, this is also the age for peak sensitivity to histoplamin.[12] Disciform lesions occur more often in men, perhaps because men are, on average, more reactive to histoplasmin than women.[12] Disciform disease is more common in whites than blacks, but there is no known difference in histoplasmin sensitivity between the 2 races. Atrophic scars are as common, if not more common, in blacks than in whites.[13] Pulmonary calcifications appear to be associated with an increased risk of disciform macular disease developing in people with OHS.[12]

There is a lower rate of fellow eye involvement in patients with disciform scars secondary to OHS than in other conditions associated with choroidal neovascularization, such as age-related macular degeneration. The estimated annual incidence rate for the development of disciform lesions in fellow eyes is 1.5% to 2.0%.[3,5,9] The comparable rate of vision loss in the fellow eyes of patients with age-related macular degeneration is 5% to 10% per year.[14] The incidence of bilateral disciform macular disease in OHS is approximately 20%.[2,5] Bilateral maculopathy is more common in men than women,[3] perhaps because of the tendency for men to have stronger reactivity to histoplasmin.[12] Hawkins and Ganley[9] reported that none of 8 fellow eyes followed up for 15 years had a disciform lesion, although 5 of the 8 exhibited 1 or more perimacular atrophic scars. The conclusion was that individuals who already have a disciform lesion in 1 eye are at low risk of for a disciform lesion in the fellow eye.

Laser photocoagulation delays or curtails loss of visual acuity in eyes with juxtafoveal and extrafoveal choroidal neovascular membranes secondary to OHS.[15] However, there is no clear benefit of laser photocoagulation for subfoveal neovascularization.[16] Therefore, alternative therapies have been sought for these patients. One of the latest developments in this area is photodynamic therapy. Although prospective, randomized clinical trials of photodynamic therapy in OHS with subfoveal neovascularization have not yet been performed, early reports are promising.[17,18] A recent report found no benefit of submacular surgery for subfoveal neovascularization associated with OHS,[19] and preliminary reports of macular translocation surgery in patients with OHS have had mixed results.[20]

Medical treatment of disciform lesions in patients with OHS has been disappointing. Anti-inflammatory, antiangiogenic, and antifungal treatment strategies have been attempted. Steroids have long been advocated as a way of controlling acute recurrences of histoplasmic maculopathy, both for their anti-inflammatory activity and their antiangiogenic properties. Atypical lesions that appear on clinical and angiographic examination to be inflammatory in nature rather than neovascular often are treated with a course of oral prednisone, although the efficacy of this approach has never been examined by clinical trials. Martidis et al.[21] reported that oral prednisone and subtenon's triamcinalone injections are effective in stabilizing, but not improving, the vision of patients with subfoveal choroidal neovascularization. The investigators concluded that corticosteroids may be valuable in managing neovascularization in patients who are awaiting other interventions, in preventing recurrence after subfoveal surgery, or in treating nonsurgical candidates. Other antiangiogenic agents, such as anecortave acetate,[22] are under investigation and may eventually prove to be of value in treating OHS patients with subfoveal lesions. There are no published reports that have found antifungal therapy to be effective in the treatment of maculopathy secondary to OHS.

Etiology of ocular histoplasmosis

OHS is found predominantly in those geographic regions in which Hc is endemic. The Mississippi and Ohio River valleys in North America contain the highest known prevalence of histoplasmosis in the world as measured by histoplasmin skin test sensitivity.[23] In endemic regions, over half of the population will have been infected by the fungus by the third decade of life.[12] Infection occurs by inhalation of airborne mycelial fragments and microconidia from the soil and is probably not transmitted from person to person nor from animals to humans.[1] Upon exposure to 37°C, fungal growth occurs as the mycelia and conidia enter the pathogenic yeast phase, which initiates a primary fungal pneumonia. Immunocompetent individuals develop a mild, usually self-limited flulike pulmonary infection; the most common symptoms are headache, cough, and myalgia. It is believed that during the course of this initial exposure, the fungus will migrate lymphohematogenously to other sites within the body, including the spleen, liver, and choroid, where the organism incites a granulomatous inflammatory reaction that, in most cases, rapidly destroys the fungus.[1] It is believed that the atrophic chorioretinal scars characteristic of OHS develop as the granulomas resolve.[24]

A progressive and potentially fatal disseminated histoplasmosis infection can develop in young children and immunocompromised individuals. In the eye, these patients

may develop a panophthalmitis. The atrophic and disciform scars characteristic of OHS will not develop in these patients, suggesting that a normal immune system is required for the development of OHS.[25]

Animal models and laboratory studies

The strongest evidence linking OHS to Hc comes from animal and laboratory studies. Histopathologic studies have found evidence of Hc in the enucleated eyes of patients with OHS. A review of the literature documenting Hc in the eye has been published by Scholz et al.[25] They reported on 6 cases in which either cells consistent with Hc or immunopathologic evidence of Hc antigen has been found in eyes of patients with OHS. Lymphocytic infiltration of clinically dormant peripapillary, macular, and peripheral lesions are often reported.[25] More recently, Spencer et al.,[26] using molecular analysis techniques, found evidence of Hc antigen in macular and peripheral scar tissue of a patient with OHS.

Two animal models of OHS have been developed. Wong et al.[27] induced a multifocal choroiditis by infecting rabbits with Hc spores and Smith[6] reported on a monkey model of OHS. Smith found that infecting monkeys with Hc induced an acute multifocal choroiditis with rapid spontaneous resolution and disappearance of the organism from the eye within 6 to 12 weeks. Most acute lesions evolved into atrophic chorioretinal scars that resembled those found in humans. However, some of the acute lesions disappeared completely, being undetectable either clinically or by flourescein angiography. None of the animals had a disciform lesion. Late reactivation of scars did not occur naturally; however, after resolution of the acute choroiditis, intracarotid injection of heat-killed Hc produced reactivation of the choroiditis. Heat-killed Hc did not produce a choroiditis in previously uninfected animals, suggesting that the monkeys had become sensitized by the initial exposure and that antigen alone (dead organisms) were then sufficient to trigger a choroiditis. Enucleation performed years after the initial infection found collections of lymphocytes in the choroid below atrophic scars and beneath normal-appearing retina at sites of disappearing acute choroiditis lesions. This finding may correlate with the so-called *de novo* lesions that seem to arise from regions of normal-appearing retina in humans. These lesions may arise from a chronic smoldering choroiditis manifested by foci of lymphocytes that occur in the choroid. Although Hc was not found in the eyes of these animals 6 to 12 weeks after infection, residual Hc antigen may persist long afterward.

Epidemiologic studies

Epidemiologic studies of localized outbreaks of acute histoplasmosis have identified moist surface soil as the natural habitat of Hc.[1] Fertilization of the soil with bird and bat droppings, particularly chickens and starlings, enhances growth and multiplication of the fungus.[28]

Several epidemiologic studies have linked Hc with OHS. A survey of medical schools found a geographic relationship between clinically diagnosed ocular histoplasmosis and sensitivity to the skin test.[29] Prior infection with Hc can be confirmed by a positive response to the histoplasmin skin test; however, this response will wane with age.[12] The test is performed by injecting a small amount of histoplasmin antigen intracutaneously and measuring the resultant induration. Population surveys in endemic regions of the United States have found that individuals with peripheral atrophic scars characteristic of OHS will more frequently have a positive histoplasmin skin test reaction, and a larger mean induration than those without such fundus scars.[7,12] On average, 90% to 95% of individuals with OHS have a positive skin test result. Additionally, 81% of patients with a disciform lesion have pulmonary calcifications typical of histoplasmosis.[30] Studies of lymphocytic transformation showed a greater response to histoplasmin antigen in patients with the disciform lesion compared with controls.[31,32]

An association between OHS and histocompatibility antigens has been reported. HLA-DR2 was present in 81% of OHS patients with macular scarring and 62% of those without a disciform lesion compared with 28% of the normal population.[33] Meredith et al.[34] reported that HLA-B7 is found more often in OHS patients with a macular disciform lesion, but not in OHS patients without maculopathy. They concluded that there may be a genetic predisposition in some patients to develop maculopathy after infection with Hc. A positive association between the HLA-DR15/HLA-DQ6 haplotype and development of choroidal neovascular lesions in patients with OHS has been reported.[35] These findings suggest that human genetic differences influence the development and course of OHS.

Epidemiologic studies provide convincing evidence that Hc is the etiologic agent responsible for OHS; however, some controversy remains. The main source of controversy arises from cases of OHS in which no linkage to Hc can be found. For example, in Europe[36] and the Northwestern United States,[37] areas in which Hc is not endemic, a syndrome clinically similar to OHS has been observed. These patients do not have circulating antibodies directed against Hc nor can any relationship with the fungus be found. It has therefore been suggested that the clinical picture of OHS may represent a "final common pathway" that can be triggered by any number of etiologic agents.[36]

Pathogenesis of ocular histoplasmosis

Although there is clear evidence that Hc is responsible for OHS, at least in endemic regions of the United States, there is considerable controversy surrounding the pathogenesis of the disease.[14] One of the key unanswered questions is what triggers the formation of disciform lesions. Because the disciform lesion is responsible for vision loss in patients with OHS, understanding the pathogenesis of this lesion is

key to preventing vision loss. Several theories have been proposed and are summarized below.

Reinfection

The reinfection theory proposes that Hc reinfects the choroid after recovery from the initial infection.[38] The source of subsequent infection could be environmental or from pockets of latent organisms in the choroid or elsewhere in the body. Because active maculopathy does not worsen when treated with corticosteroids and does not improve when treated with antifungal agents, reinfection does not appear to play a primary role in the development of disciform lesions.

Altered structure

The altered structure theory argues that histoplasmosis does not play a direct role in the development of the disciform lesion. Instead, the initial choroiditis sufficiently damages Bruch's membrane so that it is predisposed to vascular decompensation at some later point in time.[2] It is known that there typically is a delay of 10 to 30 years from the time of the onset of OHS to the appearance of a disciform lesion.[12] It is not clear why a delay would occur if a predisposing defect develops at the time of initial exposure. Choroidal neovascularization is known to develop in children and young adults from other causes such as myopia, angoid streaks, optic nerve drusen, toxoplasmosis, and Best disease.[39]

Inflammation

The inflammation theory suggests that a chronic smoldering choroiditis persists at the site of the initial focal choroiditis, gradually destroying the overlying retinal pigment epithelium and Bruch's membrane until choroidal neovascularization occurs.[14] The inflammation may be secondary to long-term persistence of fungal antigen in the choroid.[26] Over time, this may cause the appearance of atrophic scars to change and lesions that were previously undetectable to become clinically apparent. If inflammation plays an important role, one might expect intensive steroid therapy to be effective in treating acute maculopathy. However, most patients with active macular disease do not respond to intensive steroid therapy. It is possible that by the time steroid therapy is instituted (usually after an active disciform lesion has appeared) the disease process has progressed beyond the point at which anti-inflammatory agents can benefit.

Each of the above mechanisms may play a role the pathogenesis of the disciform lesion. Although the initial choroiditis may damage Bruch's membrane, it rarely, if ever, is sufficient to trigger choroidal neovascularization. Then, in genetically susceptible individuals, a chronic low-grade inflammatory response may further degrade Bruch's membrane, perhaps exacerbated by repeated exposure to Hc in the environment. Over time, Bruch's membrane may become sufficiently compromised that choroidal neovascularization develops as a nonspecific response.

Guidelines for patients at risk

Because current treatment options do not prevent severe vision loss in many OHS patients, there remains a need for effective preventative measures. Although there is currently no proven effective means of preventing the onset of macular disease in patients with OHS, it is possible to propose measures that may delay its progression.

A public education campaign in endemic regions to inform the general population about the risks posed by histoplasmosis and the measures that can be taken to minimize exposure could favorably impact the infection rate. Educating the public about high-risk behaviors for exposure to histoplasmosis and effective precautions could decrease the infection rate or delay exposure until later in life. Research on a histoplasmosis vaccine is ongoing,[40] and, once available, widespread use of this vaccine in hyperendemic regions should be encouraged.

Eye care clinicians can identify OHS patients who are at risk for vision loss. Those patients with atrophic scars in the perimacular region, especially those near the fovea, should be considered at risk for vision loss. Because atrophic scars may arise *de novo*, it is advisable to periodically monitor all patients with OHS for the development of new perimacular scars.

Patients who are at risk for vision loss need to be made aware of their risk status and given special instructions. All patients who are at risk for choroidal neovascularization should be trained in self-monitoring their vision with an Amsler grid. Beyond that, we propose that these patients be given instructions on how to avoid reinfection with Hc (*see* Table). We acknowledge that it is not at all clear that reinfection plays any role in disease progression. However, animal studies have shown that re-exposure to Hc antigen can trigger choroiditis.[6] Because reinfection could thereby presumably hasten the progression of the disease in susceptible individuals, it seems prudent to educate patients regarding measures that they can take to minimize exposure to Hc. Although complete avoidance of Hc in hyperendemic regions may be impossible, it is possible to identify and avoid those situations in which exposure to a larger innoculum is more likely to occur.[28]

It has been suggested that chronic systemic fungal infections may predispose or trigger the reactivation of atrophic chorioretinal scars in susceptible patients with OHS.[11] Aggressive treatment of dermatomycoses, onychomycosis, vaginal candidiasis, and other chronic fungal infections may be of benefit. One rationale for this approach may be that there are antigenic similarities between these fungal species such that inflammation directed against a remote fungal infection could trigger reactivation of ocular lesions.

Table Guidelines for patients at risk[6,11,12,23,25-28,39]

How can I avoid the disease?	***Protect yourself from or avoid the following high-risk areas:***
	• Bat caves • Chicken coops • Dead trees • Old buildings • Research laboratories • Aviaries • Decayed wood piles • Contaminated chimneys • School yards • Ship hatch covers
	Protect yourself from or avoid the following activities:
	• Disposing of bird waste • Construction and demolition • Working with poultry • HVAC installation or service • Bridge inspector or painter • Building restoration • Chimney-sweep • Roofer • Farmer • Gardening • Pest control • Spelunking
How do I protect myself?	***Dust control***
	• Wetting contaminated material with a water spray • Vacuum cleaning with a high-efficiency filter
	Personal protective equipment
	• Use a National Institute of Occupational Safety and Health-approved respirator • Wear disposable protective clothing, shoe coverings, and hoods
	Be aware of endogenous factors
	• Seek medical treatment of chronic fungal infections • Avoid LASIK

A patient with OHS was reported to have choroidal neovascularization after laser *in situ* keratomileusis (LASIK).[41] Others have reported nonfungal choroidal neovascularization after LASIK in age-related macular degeneration and pathologic myopia.[42] It appears, therefore, that this may be a nonspecific reaction to the procedure and not peculiar to OHS. Nonetheless, patients with OHS considering LASIK surgery should be informed that the procedure could trigger choroidal neovascularization.

Summary

The chorioretinal lesions of patients with OHS change over time, and evidence suggests that this is caused by chronic low-grade inflammation. In some patients, this may lead to a breakdown of Bruch's membrane and choroidal neovascularization. Those patients at highest risk for the development of choroidal neovascularization include white men aged 30 to 45 years with perifoveal atrophic scars in one eye and a disciform lesion in the fellow eye and with pulmonary calcifications found on radiographic studies. Elevated levels of circulating fungal antigen may worsen this inflammation and hasten the progression of the disease in genetically susceptible individuals. Therefore, when a patient with OHS presents clinically, especially if the patient is deemed to be at risk for the development of maculopathy, it is prudent to educate the patient about measures that can be taken to minimize exposure to fungal antigen.

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