Reactivation of Inflammatory Lesions in Ocular Histoplasmosis

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Background: Active inflammation has not been traditionally associated with the ocular histoplasmosis syndrome.

Objective: To investigate the occurrence of presumed inflammatory chorioretinal lesions in patients with the ocular histoplasmosis syndrome.

Methods: Patients seen with acute symptoms and a clinical picture of ocular histoplasmosis were observed prospectively between August 13, 1993, and December 2, 1997. Symptoms, visual acuity, and fluorescein sodium angiography were used to document changes in inflammatory loci.

Results: Twelve patients were seen with active inflammatory lesions. Eleven had resolution of the loci with lessening of symptoms and improvement in acuity and angiographic findings. A typical subretinal neovascular membrane developed in 1 patient 8 months after the onset of symptoms.

Conclusions: Inflammatory chorioretinal lesions can reactivate in the ocular histoplasmosis syndrome. In most of these patients, neovascularization did not develop and visual acuity was preserved.


The ocular histoplasmosis syndrome (OHS) has typically included atrophic choroidal lesions, peripapillary scarring, and the absence of vitreal inflammation.1,4 Choroidal neovascularization is the common cause of loss of vision in involved eyes and is estimated to occur in up to 5% of affected eyes.3,5 Gass and Wilkinson 4 have reported that patients observed for an extended period can demonstrate enlargement of previous scars and even the development of new ones. Palvolgyi et al6 have shown in a primate model of OHS that inflammatory lesions can reactivate. The Macular Photocoagulation Study Group7 recently reported the results of a 5-year follow-up of fellow eyes in patients with OHS. In a retrospective review of photographs before the development of choroidal neovascularization, “atypical” histoplasmosis lesions were noted. It is unclear what these atypical spots represent. This report provides an extended follow-up of patients with OHS who had an acute reactivation of presumed inflammatory loci.

The Table shows the characteristics of the patients. The mean age was 50.1 years (range, 16-74 years). Of the 12 patients, 7 were women. The patients had a documented diagnosis of OHS for a mean of 10.9 years (range, 1.1-28.7 years). The mean follow-up of the study was 2.1 years (range, 0.9-3.7 years).

The mean acuity on presentation was 20/100 (range, 20/20-20/400) in the affected eye. The mean final acuity in the affected eye was 20/60 (range, 20/20-20/400). Seven patients had more than 2 lines of improvement in their acuity, and 4 patients maintained good acuity in the affected eye with resolution of their symptoms. Only 1 patient (patient 5) lost significant acuity during the study. This patient initially improved, but 5 months later his symptoms recurred and a lesion developed into a typical subfoveal neovascular membrane during a 3-month period.

The mean acuity in the fellow eye was 20/170. Each of the decreased acuities in the fellow eye was from previous choroidal neovascularization.

Of the 12 patients, 6 had myopia. Eight of the patients had only 1 episode during the follow-up. Three patients had 2 separate episodes during the follow-up, and 1 patient had 3 separate episodes.

Of the 12 patients, 7 had a history of onychomycosis or recurrent vaginal yeast
infections. Because of this, they were treated with itraconazole. Of these 7 patients, 3 were treated with oral prednisone at the beginning of their course before being seen by us; the steroid dosage was rapidly tapered. The remaining 5 patients without a history of systemic fungal infection were also treated with itraconazole because they did not show a prompt response to steroid administration or had previously lost vision in the fellow eye despite corticosteroid treatment.

Six patients had documented evidence that the active inflammatory lesion had been present previously as an inactive scar. Figure 1 shows the course of patient 3 and highlights the characteristics of these patients. A photograph of the left eye in May 1988 (Figure 1, A) shows 3 atrophic lesions temporal to the fovea. The patient underwent laser photocoagulation in his right eye in April 1989 for a typical choroidal neovascular membrane. He was seen in July 1994 with a “spot” in his left eye for 3 weeks. Acuity was 20/70 OD and 20/25 OS. He had an atrophic scar in the right eye (Figure 1, B). One of the spots next to the fovea in his left eye was significantly larger (Figure 1, C) and had lost its sharp borders. The angiogram demonstrated active leakage at this site (Figure 1, D and E). Oral prednisone at a dosage of 40 mg/d was started and then tapered over 1 week. A regimen of oral itraconazole was also started, which was continued for 2 months at a dosage of 100 mg twice a day. He noted gradual improvement during the next month. The pa-
Figure 1. Patient 3. A, The left eye in May 1988 shows 3 atrophic lesions just temporal to the fovea. B, The right eye in July 1994 shows an atrophic laser treatment scar. C, The left eye in July 1994 shows enlargement of an inferior lesion (arrow). Early (D) and late (E) phases of angiography show the inferior lesion as a hyperfluorescent spot with leakage. F, In October 1994 there was resolution of the lesion in the left eye (arrow). Early (G) and late (H) angiography shows staining of the inactive scar without any leakage.
tient later reported that a chronic fungal infection of the toenails had cleared while he was taking the itraconazole. Figure 1, F through H, shows the color and angiographic appearance 3 months after onset. There is no longer any evidence of active inflammation. Acuity was 20/80 OD and 20/20 OS.

Five patients had no previous photographs to determine whether the active spot had been present previously. One patient (patient 5) had photographic and angiographic evidence that the inflammatory lesion was new. Figure 2, A and B, shows the patient’s right eye in July 1985. There is no macular lesion visible on the photograph or angiogram. At that time, he had an extrafoveal neovascular membrane in his left eye that was successfully treated with laser. He was seen in August 1995 with new symptoms in his right eye. Acuity was 20/60 OD. He also reported a chronic fungal infection of the toenails. There was a new lesion present in the right eye and an atrophic scar in the left eye (Figure 2, C-F). The new lesion in the right eye was poorly defined and did not resemble a typical neovascular membrane. A regimen of itraconazole, 100 mg twice a day, was started. During the next month, the patient had improvement of his vision to 20/30. The dosage of itraconazole was decreased to 100 mg/d. In December 1995 the patient thought his vision was stable, and his acuity measured 20/25+2. The itraconazole was stopped. Three months later, a classic subfoveal neovascular membrane developed in the right eye. Acuity decreased to

Figure 2. Patient 5. A, The right eye in July 1985 shows no lesion in the macula, and this is confirmed on the angiogram (B). Both eyes (C and D) in August 1995 show a new white-yellow lesion in the fovea of the right eye and atrophic scar in the left. Early (E) and late (F) phases of angiography show a poorly defined hyperfluorescent lesion with leakage in the right eye.
Gass and Wilkinson[7] previously reported the results of follow-up of 81 patients with OHS. Only 1 of these patients had a new histoplasmosis lesion develop during a 7-year follow-up. During this time, 11 patients had enlargement of an existing lesion, as determined by a comparison of color photographs. Patient 5 in this report had angiographic evidence of the development of a new histoplasmosis lesion. Rivers et al[8] described 2 patients with OHS who were seen with metamorphopsia. Both patients had poorly defined neovascularization, but typical choroidal neovascularization developed within a short period. The authors concluded that ill-defined lesions seen on fluorescein angiograms probably represented early neovascularization. They also did not have a permanent deleterious effect on vision that would be typical of untreated neovascularization. Perhaps these patients represent only a subset of patients with OHS.

Smith and colleagues[9,10] have contributed substantially to our understanding of OHS with an experimental primate model. Smith et al[10] initially demonstrated that typical lesions of OHS could be produced in monkeys following the intravenous administration of live Histoplasma capsulatum. Palvolgyi et al[11] subsequently reported that inflammatory reactivation occurred in ocular histoplasmosis lesions when these same monkeys were administered antigen only. This report was the stimulus for our investigation.

Many ophthalmologists think of OHS as a static condition in which neovascularization develops at the site of previous scars. The course of our patients indicates that inflammation does indeed recur in humans with OHS. This can result in enlargement of an existing lesion and the formation of a new lesion. If the active lesions in our patients represented early neovascularization, then there was an unusually rapid regression of these neovascular membranes. They did not appear to be typical neovascular lesions for other reasons as well. They lacked a sharp border in the early phase of angiography and did not have a fine mesh or branching structure. In addition, they did not follow a typical course for neovascular membranes. They quickly became quiescent without laser treatment. They also did not have a permanent deleterious effect on vision that would be typical of untreated neovascular membranes.

Perhaps these patients represent only a subset of patients with OHS. Previous studies[11,12] have shown a genetic association in patients with OHS. Both HLA-DRw2 and HLA-B7 have been found in a high percentage of patients with OHS. [11] In addition, HLA-B7 appeared to be related to the presence of disciform scars. [12] Several, but not all, of our patients had a chronic fungal infection of the foot or a history of recurrent vaginal yeast infections. We could speculate that these patients have some immunologic or genetic inability to eradicate fungal infections. We could also speculate that the peripheral fungal infection may somehow trigger an immune response leading to the reactivation of ocular inflammation. This was the rationale in initially treating these patients with itraconazole.

One of the more important questions raised by this report is whether it is possible to prevent neovascularization and its subsequent effect on vision. It is not possible from this small group of patients to determine the efficacy of intervention. Neovascularization developed in only 1 of 12 patients during an extended period. It cannot be said whether these presumed inflammatory lesions would have resolved spontaneously. The previous course of the fellow eye in our patients suggests that these patients are at considerable risk of vision loss. Only a large randomized study of patients with OHS will determine the efficacy of any treatment. The purpose of this study was to document that active inflammation occurs in OHS. We can speculate that there is a potential to prevent neovascularization in some patients with OHS, if we can determine a treatment that is effective for inflammation and the patients are seen early in the disease. Patients with known OHS should be encouraged to use an Amsler grid regularly. This may allow earlier detection of an active process. It is hoped that further study will allow us to determine the correct therapeutic intervention.

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REFERENCES


