

Presumed Ocular Histoplasmosis Syndrome

Case

A 33 year old female referred for assessment of bilateral choroiditis, diagnosed 4 years prior to presentation.

History

Our patient first reported visual symptoms 7 years prior to presentation to us, when she developed a small, well demarcated area near the central visual field of her right eye. Within this area, continuous movement was observed by the patient, described as a flickering sensation, similar to snow or static on a television screen. After a few days, she noticed this area beginning to increase in size, gradually losing its flickering quality and becoming more opaque instead. Examination at that time was unremarkable, blood tests, which included a CBC, sedimentation rate, RPR, and ANA were either normal or negative.

This visual field defect very gradually decreased in size without treatment, so within a two-year period, the scotoma had completely disappeared. Unfortunately, almost identical symptoms developed very shortly thereafter in the left eye. The only difference being that the defect enlarged more rapidly than before and the ultimate degree of central visual loss was much more profound.

A presumptive diagnosis of optic neuritis was made, and the patient was treated empirically with IV methylprednisolone, 1 gram a day for 3 days, followed by oral Prednisone. Vision in the left eye rapidly improved, and based on the findings of an acute onset of paracentral scotomas, photopsia, decreased visual acuity, and trace to 1+ cells in the vitreous (many of which were pigmented), and a fine granular appearance of the fovea, a diagnosis of recurrent multiple evanescent white-dot syndrome (MEWDS) was made elsewhere. Dense areas of chorioretinal atrophy, vertically placed, were also observed just temporal to each disc, as well as a subtle hypopigmented dot on the OD fovea and a punched out hypopigmented scar superior to the fovea, OS, at that time. Multiple small discrete white lesions, typical of MEWDS, however, were not seen at the RPE level; this and the patient's response to steroid in our opinion, detract from the diagnosis.

Three years later, the patient was examined when she failed a driver's test. Visual acuity OS had dropped to 20/250, and a subretinal neovascular membrane extending under the fovea was found in the left eye with one to two punched out lesions in the periphery. Examination of the right eye revealed an atrophic hole temporally with a few small hypopigmented spots in the mid-periphery. Given the punched-out appearance of the lesions and previous history of vitreous cells, a diagnosis of multi-focal choroiditis and panuveitis was considered, and the patient was referred to Dr. Foster.

Examination

Va 20/20 OD, 20/125 OS

External Examination: WNL

Orthophoric, EOM full, PERRL

VF: full OU

SLE: WNL OU

IOP: 13 mmHg OU

Fundus Examination

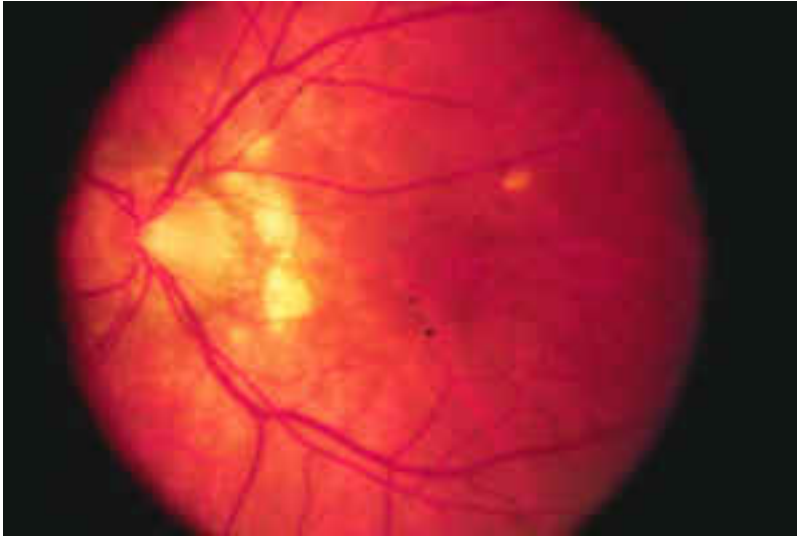


Fig.1
Fundus photograph, OS, showing dense peripapillary chorioretinal atrophy and a well defined hypopigmented scar superior to the fovea, 5 years prior to presentation to us.



Fig. 2
Fundus photograph, OS, at the time of presentation to us. A subretinal neovascular membrane is now apparent extending under the fovea.
Fluorescein Angiography

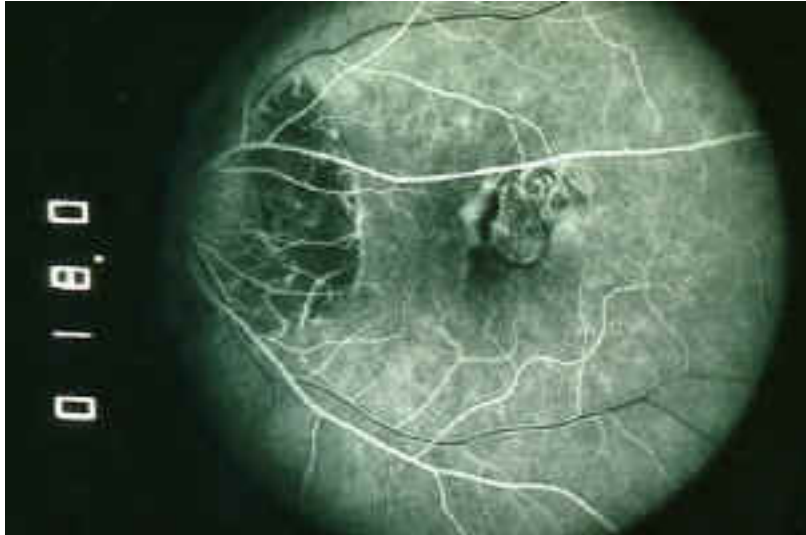


Fig. 3
Fluorescein angiogram, OD, showing marked peripapillary atrophy.



Fig. 4
Fluorescein angiogram, OS, demonstrating peripapillary atrophy and the subfoveal neovascular membrane arising from an area of RPE defect.

Further questioning revealed that the patient lived in Morrisville, Pennsylvania until her senior year at high school, and then moved to Chicago.

Assessment

A diagnosis of Presumed Ocular Histoplasmosis was made despite the fact that vitreous cells were believed to have been seen at some point in the past, given the fact that pigment cells can sometimes be taken for inflammatory cells in POHS, the presence of typical choroidal and macular lesions, and the fact that she had lived the first eighteen years of her life in an area endemic for Histoplasma, this diagnosis was considered most likely.

Plan

The patient was given instructions on regular Amsler grid monitoring and ophthalmic evaluation, with regular ICG and fluorescein angiography monitoring to detect early foci of active choroidal inflammation.

Presumed Ocular Histoplasmosis Syndrome (POHS)

Introduction

Ocular abnormalities associated with histoplasmosis were first described by Reid et al in 1942 (1), based on findings in a patient dying of acute disseminated histoplasmosis. Since then, the presumed ocular histoplasmosis syndrome (POHS) has become a generally accepted clinical entity. An interesting note, however, is that to date, there have been only nine published reports of identification of *H. capsulatum* in ocular tissue, and of these nine, two are challenged by other investigators.

Historical Background

Almost a decade after the initial description of ocular histoplasmosis, Krause and Hopkins in 1951 reported a patient with atrophic chorioretinal lesions with retinal pigment epithelial changes and hemorrhage, a positive histoplasmin skin test, and chest x- ray showing calcified lung nodules (2). In 1959 this was followed by a series reported by Woods and Wahlen who, in addition to the 'peculiar and consistent pattern of ocular lesions' described above, found cystic lesions in the macula as well (3). Patients with these findings were residents of an area endemic for the organism, and had similar immunologic as well as radiologic evidence of earlier systemic histoplasmosis; all 19 patients reacting positively to histoplasmin skin testing. By 1966, the syndrome was almost fully described by Schlaegel and Kenney, who demonstrated that atrophic lesions around the optic nerve were part of the clinical picture, and in 1981, the equatorial linear streak lesions, seen in 5% of patients with this syndrome, were first reported (4,5).

Clinical Features

Presumed ocular histoplasmosis is a diagnosis made on clinical observations. Although the appearance may not be symmetric at initial presentation, most cases have typical lesions in both eyes.

Histo spots

These are discrete, focal, atrophic choroidal scars in the macula or the periphery, smaller in size than the optic disc, and appear to be punched out of the inner choroids. They are mostly non-pigmented, but central pigment clumps, peripheral pigmentation, or diffuse pigmentation may be seen. Fluorescein angiography shows defects in the retinal pigment epithelium and patchy loss of choriocapillaris, with the absence of leakage and tissue staining, and therefore no evidence of inflammation. This characteristic peripheral scar usually remains unchanged for the lifetime of the patient. Linear streaks representing an aggregation of peripheral atrophic spots, may be seen, oriented parallel to the ora serrata and almost invariably in the equatorial region (5).

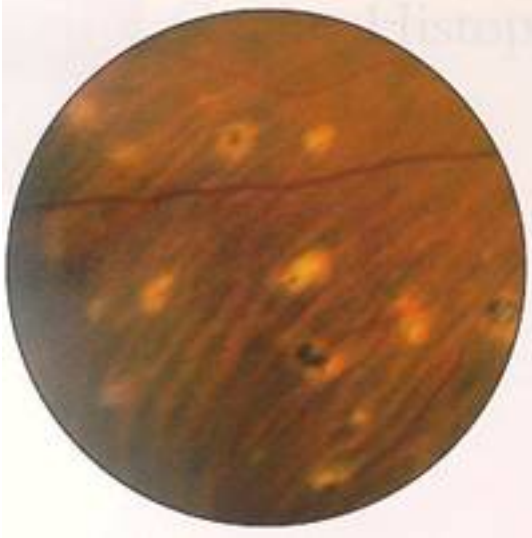


Fig. 5 Well-circumscribed, focal, punched-out areas of choroidal atrophy; typical Histo spots

Peripallary atrophy

Peripallary chorioretinal scars occur in 28% of patients with peripheral scars and no macular lesions (see below), compared with 70 to 85% in patients with macular involvement. Although

fluorescein angiography of these inactive peripapillary scars typically shows loss of pigment epithelium and choriocapillaris, hemorrhagic peripapillary choroidal neovascularization may also become evident, with permanent loss of central acuity if spread to the macula occurs (6).

Active disciform lesions

This is either choroidal neovascularization (CNV) or hemorrhagic retinal detachment in the macula, and usually appears as a gray-green lacy net on ophthalmoscopy. This is what brings a patient with POHS to the ophthalmologist, complaining of symptoms of metamorphopsia, blurred vision, or loss of central vision. Frequently, but not always, the CNV occurs at the edge of an old healed chorioretinal scar (associated with discontinuity in Bruch's membrane), although macular lesions may develop in previously normal retina as well. Emotional stress may induce serous detachment in eyes with existing CNV. A relationship may exist between histoplasmin skin testing and the activation of old macular lesions, but this contention has recently been brought into dispute. A case report of reactivation of POHS following histoplasmin skin testing and Schlaegel's review in 1974 contrast with a number of epidemiologic studies in which patients with POHS underwent skin testing with no untoward effects (26, 27, 28, 29).

Inactive disciform lesions

Resolution of active CNV or hemorrhagic retinal detachment results in these fibrovascular disciform scars at the macula. Such lesions are less than 1 disc diameter in size and white to grayish white in color on ophthalmoscopy.

Absence of vitritis

A diagnosis of POHS may only be made in the absence of cells in the vitreous and anterior segment.

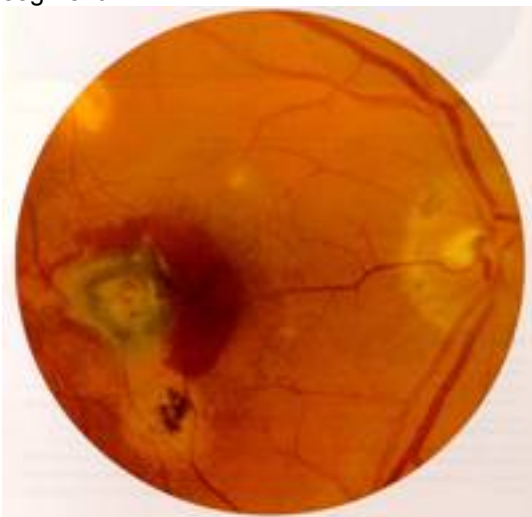


Fig. 6 Fundus photograph showing histo spots, peripapillary atrophy, active disciform lesions, and a subretinal neovascular membrane and subretinal hemorrhage.

Relationship of the ocular syndrome to systemic infection

Histoplasma capsulatum is a dimorphic fungus, existing in both yeast and mycelial phases. Occurring in the mycelial form in its natural soil habitat, the fungus is extremely resistant to physical exposure, including extremes of temperature and humidity. *H. capsulatum* is not part of the normal flora of the human body. Humans are infected by the inhalation of spores or mycelial fragments from environmental sources, usually soil associated with the excreta of bats, pigeons, chickens, and other birds. Systemic histoplasmosis is associated with large river valleys and is endemic in Central and South America, but uncommon in Europe except for a small localized region in Italy. Most cases have been recognized in the eastern and central United States, and the disease is endemic in 31 of the contiguous states of the country (7).

The parasite form of *H. capsulatum* in humans is an intracellular, oval, budding yeast measuring 2 to 4 microns. Most cases of systemic histoplasmosis are benign or asymptomatic, usual symptoms resemble a viral prodrome consisting of fever, tiredness and malaise lasting 2 to 14 days, and most cases occur during childhood. The organism may spread hematogenously to the

reticuloendothelial cells of the spleen, liver, and lungs, and in the vast majority of cases, this dissemination runs a benign, almost asymptomatic course. In immunocompromised patients, however, this becomes life-threatening, and invasion of almost every organ of the body, including the uveal tract, has been reported. Dissemination on occasion may include the uveal tract, as has been shown in patients with severe disseminated histoplasmosis (8). These cases, however, do not fit the criteria of the POHS but appeared as an endophthalmitis.

Causal or Coincidental Relationship?

The epidemiology of POHS has been studied by many investigators and yet the relationship between *H. capsulatum* infection and the manifestations of ocular disease remains an enigma. Most of the evidence in favor of POHS being caused by the organism is epidemiological, the main argument being that cases of ocular histoplasmosis frequently present to ophthalmologists in endemic areas of the United States, and rarely do outside these regions. In addition, almost all patients diagnosed with the syndrome have lived some or part of their lives in an endemic area. Positive reactions to histoplasmin skin testing are more common in patients with active disciform lesions when compared with controls, and activation of such lesions with histoplasmin skin testing has been reported.

Nevertheless, evidence refuting an etiologic relationship has been cited- as mentioned previously, the organism has never been isolated from any eye with any of the classic, pathognomic lesions of POHS. Of the nine published reports of isolation of *H. capsulatum* in ocular tissue, four cases were based on findings in young patients who died of disseminated histoplasmosis, and none had the typical quartet of POHS findings. One disputed case is of an elderly man with one disciform macular scar in one eye, two had eyes enucleated for suspected choroidal melanoma, and another had a painful infected eye that had been enucleated. The remaining case is of an immunosuppressed patient who had multiple medical problems with a post mortem diagnosis of histoplasmosis (8-16). In addition, patients with a clinical syndrome identical to POHS have been identified among people who have never traveled to an endemic area. Some reports originate from Great Britain, where *H. capsulatum* has never been identified. The possibility exists, however, that these cases represent infection by a similar, yet unidentified organism (17). The argument that amphotericin B is not effective in the ocular disorder and therefore negates an association in our opinion does not stand, since the vision threatening eye lesions develop years after the initial infection, and appear to be an immunological-mediated phenomenon (18).

Pathophysiology

The most widely accepted mechanism for this syndrome was proposed in 1972 by Gass and Wilkinson (19). According to their theory, *H. capsulatum* organisms from a single prior systemic infection disseminate from the lung to the general circulation including the choroid, as evidenced by the proved occurrence of hematogenous foci in liver and spleen during primary self-limited infection and the uveal tract in life-threatening systemic histoplasmosis. Focal choroidal granulomas develop which result in the destruction of the organism as well as small atrophic scars in the choroid and retinal pigment epithelium. Only much later, when macular choroidal neovascularization occurs as a result of these scars, do symptoms occur and these histo spots and additional components of the syndrome are detected. This appears consistent with the usual histopathologic findings of focal areas of atrophic retinal scars, with varying degrees of associated lymphocytic choroiditis. Additionally, an experimental primate model of the syndrome is induced by intra-carotid injections of yeast phase *H. capsulatum*. The chronic foci of low-grade inflammation may occur secondary to residual antigen present in such scars, and the role of this focal, smouldering, low- grade inflammation appears central to disease pathogenesis. Data on HLA typing (HLA-DRw2 more common among cases with histo spots only, and HLA-B7 and HLA-DRw2 more prevalent in disciform cases) suggest that a genetic predisposition exists, and the hypothesis that chronic, low grade inflammation in susceptible patients may trigger the development of subretinal neovascularization, and may account for de novo histo lesions as well (20). Alternatively, initial infection may lead to autosensitization, by altering the structure of retinal S antigen or other proteins and perpetuate choroidal inflammation (30). Another hypothesis is that molecular mimicry is the initiating event. The invading organism is quickly cleared, and the immune response is directed toward tissue components that are structurally similar (31).

Epidemiology

Prevalence rates of ocular histoplasmosis vary from 1.6 to 5.3 % for patients with POHS with histo spots only, and are very low for cases with active disciform lesions (0.1%). The median age of persons who have atrophic scars only is variable, since the age reported is the age at detection of histo spots by examination, not the age at which they developed in the eye, but is thought to be approximately 36 years. The median age of patients with vision threatening disciform lesions has been reported by several investigators to be in the thirties and forties (21). Cases of POHS are about equally divided between males and females, and almost all cases with disciform lesions of ocular histoplasmosis have been white.

Differential Diagnosis

Many granulomatous diseases of the fundus, such as tuberculosis, coccidiomycosis, cryptococcosis, and sarcoidosis, could mimic this syndrome. All of these entities should have obvious inflammatory activity in the vitreous, however, unlike the ocular histoplasmosis syndrome. Macular disciform lesions and atrophic peripheral punched out lesions may also occur in high myopia. Birdshot chorioretinopathy and diffuse unilateral sub acute neuroretinitis may share many of the features of POHS but are associated with vitreous cells. The two syndromes most closely simulating ocular histoplasmosis are multifocal choroiditis with panuveitis, and punctate inner choroidopathy (PIC). The former can be differentiated from POHS by the presence of vitreous cells. Choroidal scars in PIC are smaller and tend to be more confined to the posterior pole when compared to POHS. The lesions are usually active when first observed, although they do resolve and lead to atrophic scars. In the absence of vitritis and active choroidal lesions, the syndrome may be difficult to distinguish from ocular histoplasmosis, the distinguishing features of resolved PIC are the smaller size of the choroidal scars and location being confined mostly to the posterior pole.

Treatment

Because there is no evidence of any organisms present, antifungal medicine, such as Amphotericin B, has no role in POHS. No therapy is required for POHS with histo spots only; however, patients should be reminded that they are at risk for macular disease. If macular scars are present, however, patients should be followed more closely and instructed on the use and utility of Amsler grid testing at home. Any change in vision or metamorphopsia should be evaluated by an ophthalmologist in such patients. Although no data from clinical trials are available, many clinicians believe that corticosteroids have some beneficial effect in the treatment of neovascular membrane associated with this syndrome. Because argon laser photocoagulation has been shown to be beneficial when CNV is outside the capillary free zone, the use of corticosteroids (40 to 100 mg of Prednisone daily for several weeks) should be limited to situations in which the neovascular membranes are subfoveal (22).

Clinical trials have shown that laser photocoagulation can reduce the risk of severe visual loss secondary to CNV in patients with POHS. The Macular Photocoagulation Study Group, in its first trial initiated in 1979, was halted prematurely in 1983 when it became evident that argon laser photocoagulation was clearly effective in preventing or delaying loss of visual acuity in patients with extrafoveal CNV (greater than 200 micrometers from the center of the foveal avascular zone) (23). The Group initiated a second trial in 1981, studied patients with juxtafoveal CNV (1 to 200 micrometers from the center of the foveal avascular zone), and demonstrated that eyes treated with krypton laser were less likely to lose visual acuity than untreated eyes (and enrollment was halted again prematurely) (24). Sub-group analysis alleviated previous concerns that damage to the papillomacular bundle does not occur when CNV is nasal to the fovea, and therefore laser photocoagulation is not contraindicated in these POHS patients. In both trials, persistence or recurrence of CNV at the border of the treatment scar occurred in a significant number of patients (26% in extrafoveal and 33% in juxtafoveal CNV).

Management of subfoveal CNV, however, warrants a different approach. Laser treatment of subfoveal neovascularization has shown to be of no benefit in a pilot study, and since CNV membranes have variable patterns of growth and may regress spontaneously, initial photocoagulation does not seem warranted. Since 1992, however, there have been numerous reports on the surgical removal of subfoveal CNV membranes, and results appear encouraging. Initial visual improvement or stabilization of visual acuity has ranged from 37 to up to 83% of

cases, and follow up of a large number of cases seems to indicate a beneficial effect. In addition, photodynamic therapy with Verteporfin has been employed in choroidal neovascularization in one patient with POHS, in whom a significant improvement of visual acuity occurred and persisted at approximately 5 months follow-up.

Prognosis

Untreated choroidal neovascularization in the macula of patients with POHS has been shown to result in a visual acuity of 20/200 or less in about 55% of patients. Neovascularization of the fovea results in the same visual acuity in more than 75% of patients. The best final visual acuity outcome has been shown to occur in younger patients, those with a better initial visual acuity, smaller neovascular membranes, and the absence of vision loss due to ocular histoplasmosis in the fellow eye. The risk for blindness, however, is low even for patients who have bilateral macular involvement with neovascularization. The second eye becomes involved at the macular region in about 12% of cases within 5 years and 22% within 10 years after involvement of the first eye, and the presence of atrophic choroidal scars in the macula of the second eye is a much greater risk factor for developing such disciform lesions in the macula (25). If no inactive scars are found in the macula, the patient can be reassured that although macular disease in the second eye is less likely, it may occur in up to 9% of patients in a period of about 10 years.

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Presumed Ocular Histoplasmosis Syndrome (POHS)

Khayyam Durrani, M.D.

1. 1) All of the following occur in Presumed Ocular Histoplasmosis Syndrome (POHS) except:
 2. a)peripapillary crescent
 3. b)disciform lesions
 4. c)vitritis
 5. d)atrophic choroidal scars
6. 2)Each of the following may be indicated in POHS management except:
 7. a)regular Amsler grid testing
 8. b)Photodynamic therapy
 9. c)Amphotericin B
 10. d)Argon laser photocoagulation
11. 3)The following Human Leukocyte Antigens are associated with POHS:
 12. a)HLA B7
 13. b)HLA B29
 14. c)HLA DRw2
 15. d)HLA B60

16. 4) Laser photocoagulation has been shown to prevent or delay vision loss secondary to choroidal neovascularization (CNV) in each of the following except:
17. a) extrafoveal CNV (≥ 200 micrometers from the foveal avascular zone)
18. b) subfoveal CNV
19. c) juxtafoveal CNV (≤ 200 micrometers from the foveal avascular zone)
20. 5) In contrast to POHS, the following clinical features are seen in Punctate Inner Choroiditis except:
 21. a) vitreous cells
 22. b) smaller atrophic lesions
 23. c) lesions confined to the posterior pole
 24. d) no anterior chamber inflammation
25. 6) Vitreous biopsy is sometimes used to confirm a diagnosis of POHS (T/F)
26. 7) Most patients diagnosed with POHS present with a history of a flu-like illness in the recent past (T/F)
27. 8) Patients with POHS without choroidal neovascularization are usually asymptomatic (T/F)
28. 9) POHS occurs frequently in patients of African descent. (T/F)
29. 10) Histoplasmin skin testing is routinely used in the diagnosis of POHS. (T/F)
30. Answers:
31. 1) C 2) C 3) A, C 4) B 5) A 6) F 7) F 8) T 9) F 10) F