Presumed Ocular Histoplasmosis Syndrome

Richard C. Trevino, O.D., and Rita J. Taricani, O.D., F.A.A.O.

Presumed ocular histoplasmosis syndrome is an ocular manifestation of the fungus Histoplasma capsulatum *and is common in areas where the organism is endemic. The clinical picture consists of a disseminated choroiditis characterized by focal scarring, commonly referred to as histo spots; a circumpapillary choroiditis producing scarring around the optic nerve head; and an exudative maculopathy that usually occurs in middle age and that can result in severe vision loss. Diagnosis is based on the fundus appearance. Three cases that illustrate the various manifestations of this syndrome, including a unique presentation of a histo streak, are presented.*

Keywords: Presumed ocular histoplasmosis syndrome; *Histoplasma capsulatum*; histoplasmosis; choroiditis; maculopathy

Introduction

There are three distinct ocular manifestations of the fungus *Histoplasma capsulatum:* (1) histoplasmic endophthalmitis; (2) solitary histoplasmic chorioretinal granuloma; and (3) presumed ocular histoplasmosis syndrome.[1] The first two forms of ocular involvement are extremely rare. Presumed ocular histoplasmosis syndrome (POHS), on the other hand, is quite common in areas where the organism is endemic.

Histoplasmosis is a chronic infectious disease usually acquired through inhalation of fungal spores.[2] The primary focus of infection is the lungs. Over 90% of systemic histoplasmosis is benign and asymptomatic, but the disease can be serious, especially in immunodeficient patients. Histoplasmosis occurs worldwide in river valleys between latitudes 45° N and 45° S where the organism can grow in soil fertilized by bird or bat droppings.[3] In North America it is most prevalent in the Mississippi and Ohio River valley regions, where in some communities over 80% of the population have been infected by the organism.[4] In Canada histoplasmosis is commonly encountered in southern Ontario and parts of southern Quebec, but is relatively rare throughout the rest of the country.

POHS occurs in about 2.5% of individuals residing in endemic areas.[5] The term "presumed" indicates that the association between *H. capsulatum* and POHS has

From the School of Optometry, University of Waterloo, Ontario, Canada.

Dr. Trevino's address: Kaiser Permanente, 6501 Loisdale Ct., Springfield, VA 22150, USA.

Address reprint requests to Rita J. Taricani, O.D., School of Optometry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1.

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not yet been proven.[6] It is true, however, that the evidence incriminating *Histoplasma* is so overwhelming that many feel justified in eliminating the word "presumed" from the syndrome's name. The disease is considered a "syndrome" because the typical clinical picture of POHS is known to occur in the absence of any evidence of infection by *H. capsulatum*.[7-9] This suggests that organisms other than *Histoplasma* may be capable of producing the clinical picture of POHS.

There are three classic clinical manifestations of POHS: (1) disseminated choroiditis characterized by scattered histo spots; (2) circumpapillary choroiditis producing scars around the optic nerve head; and (3) an exudative maculopathy.[10] Unlike many other forms of choroiditis, POHS is not associated with vitritis or anterior uveitis. The diagnosis of POHS is made on clinical grounds through recognition of the distinctive clinical picture of the disease. All three elements of the POHS triad are not required to diagnose the disease and atypical cases are common.[11] The histoplasmin skin test can be used to determine whether a patient has been exposed to the fungus, but it has several important disadvantages: (1) up to 90% of individuals will test positive in endemic areas; (2) it may cause a flareup of a patient's maculopathy, and (3) agents other than *Histoplasma* may produce the syndrome.[3]

Differential diagnosis includes causes of multifocal chorioretinal scarring or atrophy: neuroretinitis, bird-shot (vitiliginous) retinochoroidopathy, multiple scars due to toxoplasmosis, syphilis, myopic degeneration, and the pseudohistoplasmosis syndromes.[6] There are several clinical entities that closely resemble POHS, hence the term pseudohistoplasmosis. These conditions may, in fact, be pathogenetically related to it and to one another. Two such simulating conditions are known as multifocal choroiditis[6,12] and punctate inner choroidopathy.[6,13]

Histo Spots

The typical histo spot is a discrete, round to slightly irregular atrophic choroidal scar.[11] Spot size usually ranges between 0.2 to 0.6 disc diameter. Pigment may be absent or form a clump within or at the margins of the scar. It is estimated that 84% of histo spots are found posterior to the equator. Histo spots are bilateral in 62% of affected individuals, and there is, on average, a combined total of about eight scars in both eyes.[14] Almost all histo spots, including many present within the macular region, are asymptomatic.[10]

It is thought that at the time of the original infection the organism enters the choroid via the bloodstream, initiating focal inflammatory lesions that ultimately develop into histo spots.[6,15] At this time the patient will also develop a positive response to the histoplasmin skin test. Over a period of several weeks the infection clears and the organism retreats to multiple foci of dead or latent organisms throughout the body. Although *Histoplasma* organisms normally do not appear to reside within the eye itself,[6,16] histo spot activity may persist long after the primary infection has cleared. Histo spots may change in shape and size; some lesions will fade while others will enlarge or become more dense.[10]

Circumpapillary Choroiditis

The peripapillary changes of POHS consist of discrete or confluent histo spots similar to those found elsewhere throughout the fundus. Approximately one-half of affected patients have confluent scarring around the optic disc with few discernible nodules.[3] Most peripapillary scarring is of little consequence. Schlaegel reports that circumpapillary choroiditis is asymptomatic in about 90% of individuals; the remaining 10%, however, develop a vision-threatening hemorrhagic variety that is accompanied by symptoms of metamorphopsia and visual acuity loss.[3] In these patients peripapillary histo spot reactivation leads to choroidal neovascularization and subsequent subretinal hemorrhage that usually encompasses the disc and may extend toward the macula.

Peripapillary scarring is an important clinical sign of POHS and its presence is a useful aid in diagnosis. It is present in both eyes of 70% of patients and unilaterally in an additional 15% of individuals.[10]

Exudative Maculopathy

Histoplasmic maculopathy is a significant cause of central vision loss in young adults. It is estimated that 4.5% of persons with POHS develop maculopathy, the onset of which usually occurs between the ages of 20 to 50 years.[5] Follow-up studies reveal that 12% of patients will develop symptomatic disease in the second eye within five years, and 22% will develop symptoms in the second eye within 10 years.[17,18]

It is generally believed that almost all histoplasmic maculopathy arises from a pre-existing asymptomatic histo spot located in the macular region.[10] It is theorized that reactivation of histo spots may occur in response to transient episodes of circulating histoplasmic organisms or antigens emanating from some systemic source.[11,15] It may also be triggered by re-infection with *H. capsulatum* or by histoplasmin skin testing. Reactivation of a histo spot is characterized by lymphocytic infiltration of the lesion. Over a period of years recurrent inflammation of the lesion results in growth of the spot and localized destruction of Bruch's membrane. If the lesion is located in the vicinity of the macula, it may permit invasion of the subretinal space by blood vessels from the choroid creating the potential for a disciform macular scar. This neovascular process appears to

be a response to the unique anatomical properties of the macula, which predispose it to neovascularization whenever Bruch's membrane is compromised. It is, however, possible that lymphocytic infiltration may play a direct role in the development of the maculopathy.[6]

The following case reports illustrate various clinical manifestations of POHS and describe management strategies.

Case 1

F.W. is a 51-year-old white male in good health who was first examined at our clinic in 1984. Examination at that time revealed several histo spot lesions in the posterior fundus of each eye, including histo spots adjacent to each macula. The patient was asymptomatic and vision was normal.

F.W. was next seen in 1986 when he complained of visual blur of two months duration in the right eye. Visual acuity was 20/80 (6/24) in the right eye and 20/20 (6/6) in the left eye. Amsler grid testing of the right eye revealed central distortion. Ophthalmoscopy of the right eye disclosed numerous histo spots and peripapillary chorioretinal scarring. Also present was a serous detachment of the macula and associated retinal hemorrhage. The posterior fundus of the left eye contained several histo spots and peripapillary chorioretinal scarring, but was otherwise unremarkable (*Figures 1A* and *1B*). We obtained a fluorescein angiogram that confirmed the presence of a subretinal neovascular membrane in the right eye (*Figure 1C*), but the subfoveal membrane was considered untreatable. The visual acuity in this eye has since deteriorated to ~ 100 (Feinbloom chart) while the vision of the left eye remains stable at 20/20 (6/6) (*Figures 1D* and *1E*).

Given the presence of maculopathy in one eye and histo spots in the posterior pole of the other, the estimated risk of the second eye developing maculopathy is one in four.[10] Because of the high risk for vision loss in the fellow eye, we have placed this patient on daily Amsler grid monitoring of his left eye. He is instructed to seek care immediately should he detect any changes in the vision of this eye. His progress is monitored biannually in the clinic.

Discussion of Case 1

Histoplasmic maculopathy is almost always caused by choroidal neovascularization. Occasionally, a serous macular detachment may arise in the absence of neovascularization, due to fluid leaking through a perimacular histo spot.[17] In most patients neovascularization appears to be triggered by reactivation of a histo spot located in the posterior fundus. Symptoms of metamorphopsia and vision loss ensue. Patients with histo spots in the macular region have an annual incidence of maculopathy of 3.6% compared to 1.7% for persons with POHS but without perimacular histo spots.[18] Schlaegel estimates the risk of a second eye developing maculopathy to be one in four for patients with macular histo spots, but only one chance in 50 if there are no lesions near the macula.[10]

Treatment is not indicated for inactive histo lesions.[6,12] Because atrophic scars adjacent to the macula may predispose to the development of macular detachment, they should be followed, but prophylactic treatment is not of any benefit and may actually stimulate choroidal neovascularization.[12]

Choroidal neovascularization can be treated with laser photocoagulation.[6,19] The entire lesion as defined by fluorescein angiography is treated with intense photocoagulation in an attempt to destroy the neovascular membrane. The Macular Photocoagulation Study (MPS) has found that argon blue-green laser photocoagulation is useful in preventing severe visual acuity loss when the neovascular lesion is associated with a limited amount of blood and is located 200 microns or more from the center of the foveal avascular zone (FAZ).[20] Krypton red laser photocoagulation is beneficial in lesions that have choroidal neovascularization 1 to 199 microns from the center of the FAZ, or choroidal neovascularization 200 microns or farther from the FAZ center with blood or pigment extending within 200 microns of the FAZ center.[19] The theory that allergic phenomena play a role in the development of macular detachment has lead some to use corticosteroids administered orally or locally through periocular injection.[12,21] There is little evidence to suggest that corticosteroids are of any value in the treatment of histoplasmic maculopathy. In fact, most patients fail to show any apparent response to intensive corticosteroid therapy, and neither treatment modality has any long-term value.[6] The cornerstone of effective therapy is the early recognition by the patient of the symptoms of maculopathy, which may be facilitated through daily monitoring of vision with an Amsler grid. The importance of compliance with Amsler grid use is reinforced at each office visit.

Case 2

T.S. is a 67-year-old white male who suffers from severe arthritis and hypertension. Ocular history is positive for POHS, age-related cataract, and ocular hypertension. He was seen in our clinic on referral from his family optometrist for perimetry and fundus photography.

Visual acuity was 20/40 (6/12) in the right eye and 20/20 (6/6) in the left. Acuity reduction in the right eye was attributed to nuclear sclerosis of the crystalline lens. Tonometry readings were 19 mm Hg and 22 mm Hg in the right and left eyes, respectively. Automated perimetry using the Humphrey 30-2 threshold program revealed irregular field constriction and enlargement of the blindspot for each eye

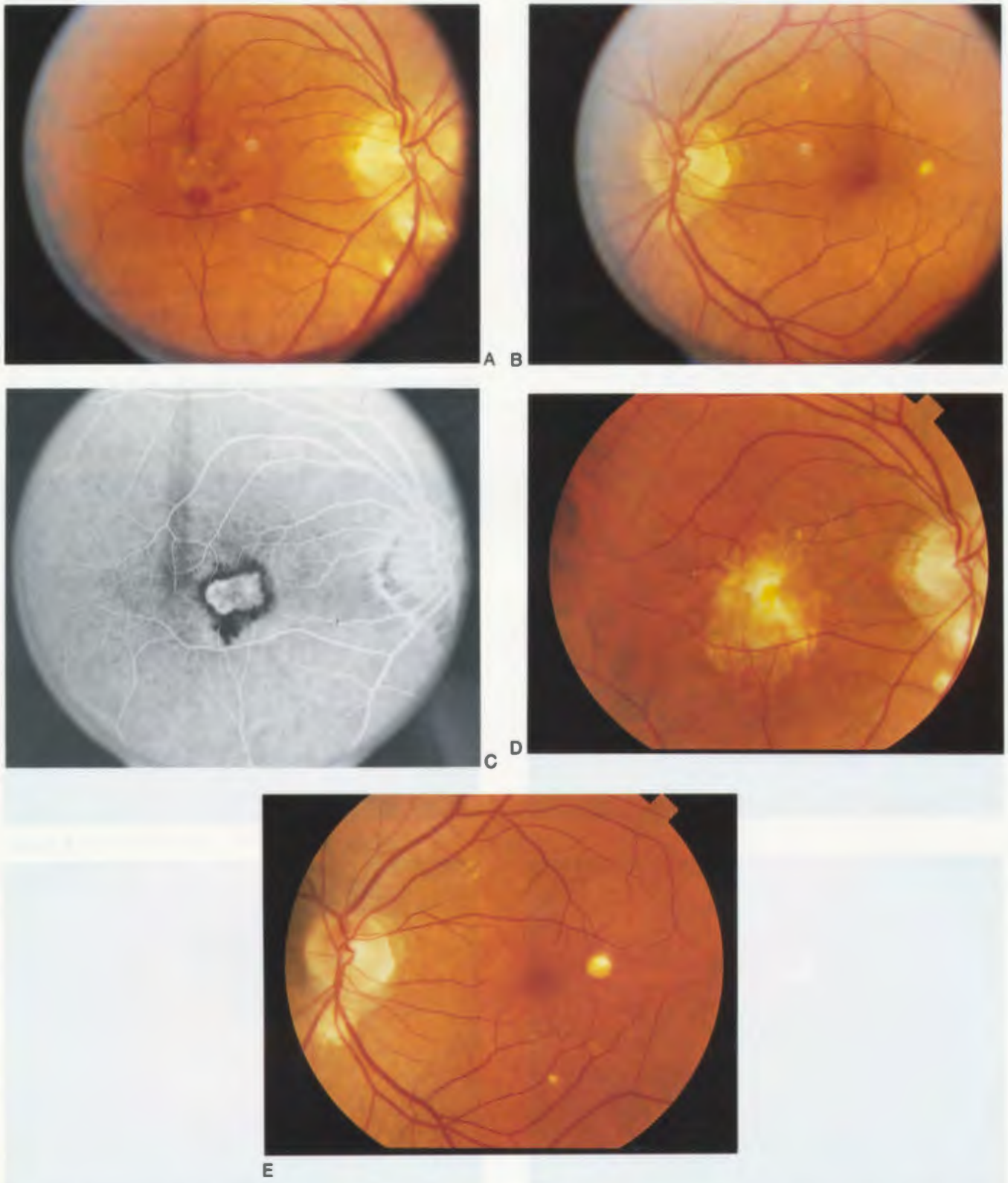

Figure 1. Appearance of the right eye (*A*) at the time of presentation with macular detachment and associated hemorrhage. Left eye (*B*). Fluorescein angiogram of the right eye (*C*) reveals presence of choroidal neovascular membrane. Disciform macular scar of right eye (*D*) three years following development of maculopathy. Note the enlargement of the histo spot located temporal to the macula in the left eye (*E*).

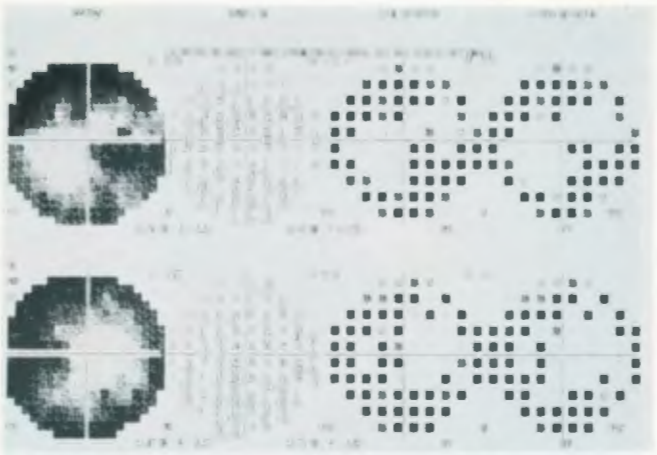

Figure 2. Automated visual fields (Humphrey Field Analyser 30-2 threshold test) for right (top) and left eyes (bottom).

(*Figure* 2). Ophthalmoscopy revealed extensive diffuse peripapillary chorioretinal scarring in each eye. There were also multiple, small "punched-out" areas of chorioretinal atrophy with surrounding pigmentary hyperplasia in the nasal equatorial region of each eye (*Figure* 3). The macula of each eye was normal. The cup-to-disc ratio under stereoscopic examination with the biomicroscope was estimated to be 0.8 in each eye.

Discussion of Case 2

This patient has three ocular conditions that require monitoring: POHS, ocular hypertension, and cataract. Although presumably unrelated, their simultaneous presence poses a special challenge to the clinician. The problem of accurately defining the cup-to-disc ratio is made more difficult

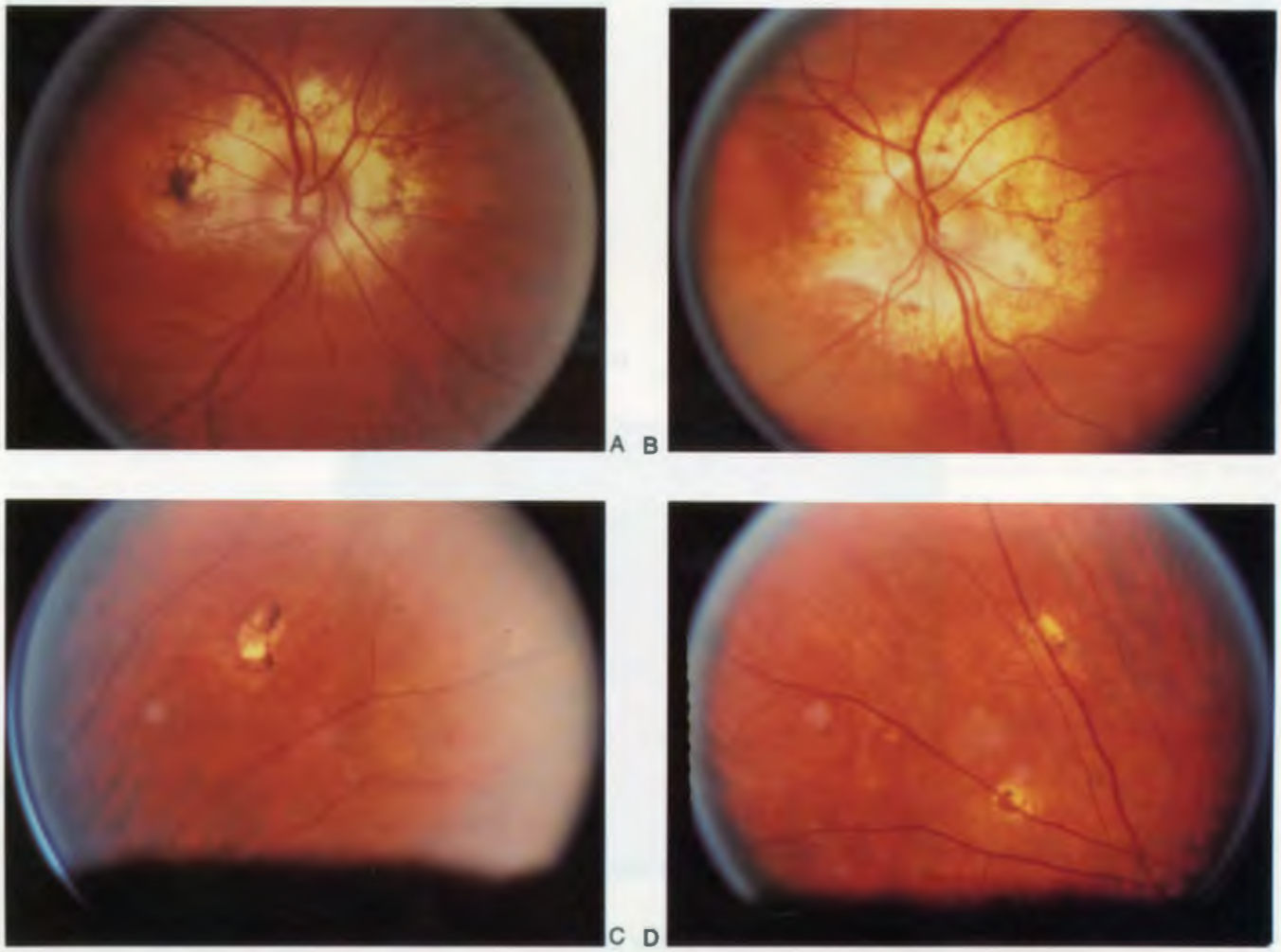

Figure 3. Right eye: optic nerve head with peripapillary scarring (*A*) and peripheral histo spots (*B*). Left eye: optic nerve head with peripapillary scarring (*C*) and peripheral histo spots (*D*).

because peripapillary choroiditis tends to obscure the disc margin. Sole dependence on the flat, highly magnified image provided by direct ophthalmoscopy for disc evaluation could lead to an underestimation of the cup-to-disc ratio, especially when the margins of the cup lie beyond the region of central pallor of the disc. Fundus biomicroscopy offers the advantages of stereopsis and flexibility in choice of magnification, making it the preferred method of optic nerve head examination.[22]

Although perimetry did not reveal any specific glaucomatous defects, this patient's visual fields were clearly abnormal. The extensive peripapillary scarring found in each eye is consistent with the enlarged blind spots found on perimetry. Enlargement of the blindspot is not a glaucomatous visual field defect;[23] therefore, this consequence of POHS should not be confused with the development of glaucoma. The constriction of each visual field is not necessarily glaucomatous. It may actually be an artifact secondary to this patient's relative inattentiveness to the test (large number of false-negative errors) or possibly a result of the patient's head drifting back from the instrument during the examination, creating a trial lens scotoma.

The primary importance of peripapillary scarring in POHS is its usefulness as an aid in making the correct diagnosis. It is present to some extent in about 85% of people with the disease.[10] Although rare, activation of peripapillary lesions can produce vision disturbance. In the so-called hemorrhagic type of circumpapillary choroiditis, subretinal hemorrhage extends toward the macula, producing symptoms of metamorphopsia and vision loss. Unfortunately, there appears to be no reliable means of predicting which patients will develop hemorrhagic circumpapillary choroiditis.[17]

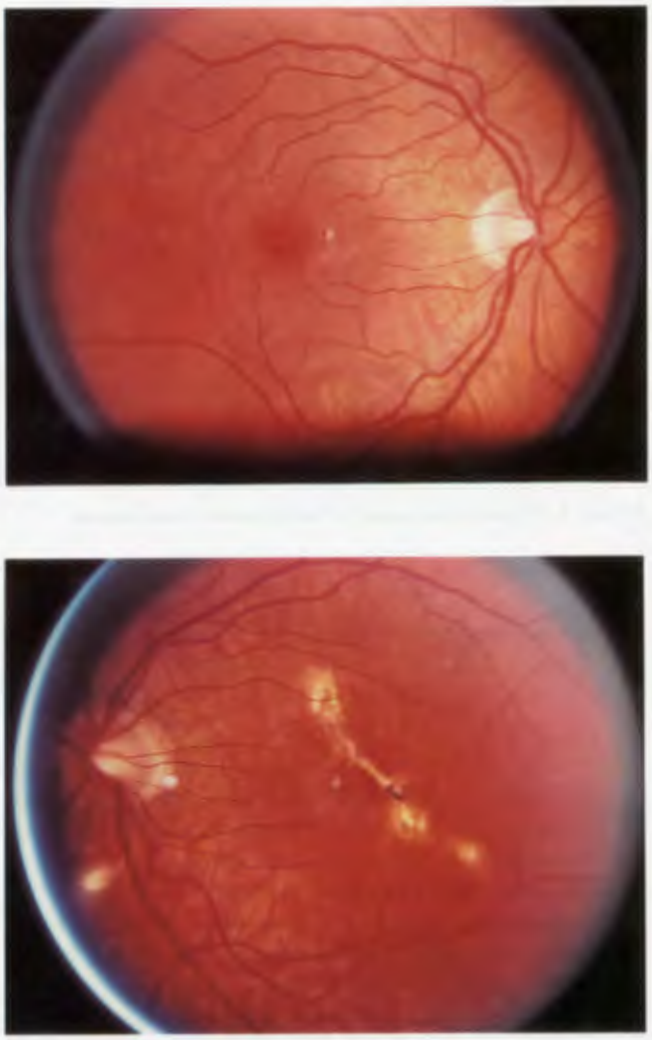

Figure 4. Right (*top*) and left (*bottom*) eyes of patient in Case 3.

Case 3

N.H. is a 23-year-old white female who presented for a second opinion as to the cause of a one-year history of decreased vision affecting her left eye. She had been seen by another eye care specialist who diagnosed myopic macular degeneration by fluorescein angiography and failed to find any evidence of subretinal neovascularization. Her refraction is OD: $-7.00-1.25 \times 030$ and OS: $-6.50-0.75 \times 160$. She denies any history of ocular trauma, and medical history is unremarkable.

Best corrected visual acuity was 20/20 (6/18) in the right eye and 20/40 (6/12) in the left eye. Funduscopic examination of the right eye revealed a temporal crescent as well as a chorioretinal disturbance on the nasal side of the disc, and a few histo-like lesions in the midperiphery. The left eye revealed similar peripapillary changes, and a vertically oriented curvilinear chorioretinal scar approximately 1.5 DD long was present in the macula. The lesion appeared to be comprised of a string of focal chorioretinal scars connected to each other by atrophic and hyperplastic retinal pigment epithelium. Several distinct histo spots were scattered throughout the posterior fundus of this eye (*Figure 4*).

Based on the clinical appearance of the fundus, a diagnosis of POHS was made. The patient was instructed on daily Amsler grid self-monitoring of her vision and placed on biannual recall. Consultation with a retinologist confirmed the diagnosis of POHS.

Discussion of Case 3

Linear aggregation of histo spots occurs in the equatorial region of about 5% of patients with POHS and are referred to as "histo streaks"[9,24,25] (*Figure 5*). Streak lesions are usu-

Figure 5. Typical appearance of histoplasmic streak lesions.

ally oriented roughly parallel to the ora serrata and are almost always located within 3 disc diameters of the ampullae of the vortex veins. They have never been reported to occur in the region of the posterior fundus. Length and pigmentation vary widely, but average length is about 3 clock hours (or one quadrant). Although most streaks are depigmented, pigmentation, when present, is usually spotty in character. The cause of streak formations is unknown.

The lesion in the macula of this patient's left eye is not a typical histo streak because of its location in the posterior fundus. Its curving nature is also not consistent with the typical presentation of streak lesions. On the other hand, because it does appear to be composed of a linear arrangement of histo spots, this lesion could conceivably represent an anomalous histo streak.

The differential diagnosis of histo streaks must include other known causes of linear fundus lesions: demarcation lines, angioid streaks, choroidal rupture, ophthalmomyiasis, and retinal lattice degeneration,[25] all of which can be distinguished from histo streaks by their characteristic appearances.

Summary

POHS occurs worldwide, and in North America is prevalent in the Mississippi and Ohio river valley regions and in southern Ontario and Quebec. Diagnosis is based on recognizing the distinctive fundus appearance, which consists of histo spots, peripapillary scarring, and exudative maculopathy. The clinician should be aware that atypical presentations of POHS commonly occur. Atrophic histo spots do not require treatment, although it is believed that histoplasmic maculopathy arises from pre-existing histo spots. The presence of such spots in the macular area, therefore, requires careful monitoring. In some instances active maculopathy may be treated with laser photocoagulation. Most peripapillary scarring is of little consequence; however, it may present a problem in accurately determining the cup-to-disc ratio.

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