Presumed Ocular Histoplasmosis Syndrome

10

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Introduction

Histoplasmosis is caused when airborne spores of the fungus *Histoplasma capsulatum* are inhaled. The lungs are the primary infection site. Unless it occurs in immunocompromised patients in whom it may mimic tuberculosis, systemic histoplasmosis often displays very mild symptoms and may even be asymptomatic. Usually occurring in children, it causes fever and malaise similar to the common cold or flu. However, despite these mild symptoms with initial infection, it can cause profound vision loss years later [1].

Presumed ocular histoplasmosis (POHS) is a choroidopathy, typically characterized by atrophic chorioretinal scars, peripapillary atrophy, and the absence of vitritis. POHS may or may not be associated with choroidal neovascularization (CNV), the primary reason for decreased vision in these patients. Rarely, histoplasmosis also can cause a histoplasmic endophthalmitis or a solitary histoplasmic chorioretinal granuloma [2]. The endophthalmitis form usually occurs in patients with disseminated histoplasmosis, and it lacks the classic lesions seen in POHS [3]. The solitary granuloma, also known as a histoplasmoma, may mimic toxocariasis and is usually seen in immunocompromised individuals.

Etiology

Over the past years, the exact origin of the disease has been debated. The most common theory is that POHS is caused by the yeast form of *H. capsulatum.* This has been demonstrated mostly by epidemiological studies. Hence the term *presumed. Histoplasma capsulatum* is a dimorphic fungus found in the soil, usually near the Ohio and Mississippi River Valleys. The fungus is strongly resistant to temperature and humidity extremes. Bird feathers of chickens, pigeons, and blackbirds carry the fungus. Bird and bat excretions have also been found to harbor the fungus. Infection occurs when the yeast is inhaled.

Reid et al. first described POHS in 1942 when a patient dying of disseminated histoplasmosis was described to have certain ocular findings [4]. Subsequently, Krause and Hopkins described a patient with atrophic chorioretinal lesions associated with a positive histoplasmin skin test and a chest X-ray showing lung nodules [5]. Later, Woods and Whalen reported a case series, describing patients with ocular lesions and

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macular cysts [6]. All of these patients were noted to live in an area endemic for *H. capsulatum* and showed evidence of prior systemic infection with histoplasmosis such as calcified lung nodules. All of the patients had a positive histoplasmin skin antigen test, signifying a strong correlation between POHS and *H. capsulatum*.

However, other evidence in the literature refutes such a definite relationship [7]. The failure to actually isolate the fungus from the eye as well as negative histoplasmin skin antigen tests in patients with classic eye findings point toward the possibility of another causative organism. While a few papers do report the isolation of *H. capsulatum* in the eye, most of these patients suffered from disseminated histoplasmosis and lacked the classic ocular findings of POHS. Another study from the Netherlands reported a series of patients demonstrating clinical signs of POHS that all had negative histoplasmin skin antigen tests [8]. Furthermore, some patients reported in the literature with classic POHS findings denied any previous habitation or travel to an endemic area [9].

HLA haplotypes DRw2 and B7 have also been connected to POHS, suggesting that POHS represents an inflammatory reaction triggered against certain organisms, one of these being *H. capsulatum.* HLA-B7 has been associated in patients with disciform scarring. HLA-DRw2 was detected in 81 % of patients with disciform scarring and 62 % of patients with peripheral histo spots [10–12].

Epidemiology

POHS is most commonly found in patients living in the Ohio and Mississippi River Valley. This area is comprised of the following states: Arkansas, Kentucky, Missouri, Tennessee, West Virginia, Alabama, Illinois, Indiana, Iowa, Kansas, Louisiana, Maryland, Mississippi, Nebraska, Ohio, Oklahoma, Texas, and Virginia. This region is also known as the "Histo Belt". In these areas, which are endemic for *H. capsulatum,* around 60–90 % of the adult population have a positive histoplasmin skin antigen test. However, only 1.5 % of patients who test positive for histoplasmin actually demonstrate clinical signs of POHS [13]. Outside the United States, it is found in Central and South America, a small region in Italy, South Africa, and Southeast Asia.

Histopathology

POHS chorioretinal lesions demonstrate no fungal characteristics when examined with light microscopy. Rather, these lesions exhibit different stages of inflammatory activity, such as mixed populations of inflammatory cells with loss of retinal pigment epithelium as well as adhesions between outer retinal and choroidal lesions. Focal aggregations of lymphocytes without disruption of Bruch's membrane may be seen [14–16]. These findings also support that POHS is not caused by an active fungal infection but by an autoimmune response to a specific antigen.

Pathophysiology

The yeast is usually inhaled in the microconidia form (<5 μm in size). It then spreads hematogenously as evidenced by foci of the organism found in the liver and the spleen. When the antigen spreads to the uveal tract, focal choroidal granulomas may result, causing an inflammatory reaction in the choroid. This subsequently leads to a chorioretinal atrophic scar. There may be residual antigen within these scars resulting in a low-grade inflammation that prompts CNV to develop. Also hypothesized is that the infection sensitizes ocular proteins or that the fungal elements are similar in structure to those in the eye, inciting an immune response against the choroid [17].

POHS is able to be replicated in an animal model. Rabbits injected with intracarotid injections of yeast exhibited signs of choroiditis within one to two days in the eye on the side that was injected. Seven to twenty days later, the fellow eye developed lesions without vitreous inflammation similar to those seen in humans

with POHS. No yeast organisms were able to be isolated in the healed granulomas after several weeks [18].

At one point, it was thought that histoplasmin skin testing might lead to the reactivation of old macular scars. However, a number of case series failed to demonstrate a clear relationship between the skin test and reactivation.

Risk Factors

Travel to or habitation in the Ohio and Mississippi River Valley is the main factor predisposing patients to POHS. Various activities that may increase inhalation of the fungus include spelunking, bulldozing, cleaning chicken coops, and raking. Patients usually present with symptoms of CNV during the second to fifth decades of life. The age may vary since patients without CNV are usually found to have POHS incidentally on a routine examination. There is no gender predilection. Patients are usually healthy individuals. Only 0.7 % of POHS patients are black, and patients with POHS and CNV tend to be Caucasian [19].

Diagnosis

History

If no CNV is present, POHS is asymptomatic. CNV is what usually brings the patient to medical attention. If CNV is present, patients will report painless vision loss, central scotoma, blurred central vision, and/or metamorphopsia. All patients should be asked details about where they have lived and traveled.

Physical Exam

POHS is a clinical diagnosis. Both eyes should be examined thoroughly because findings are bilateral in up to 60 % of cases [20]. Careful slit lamp and biomicroscopy should be performed while looking for the three classic signs of POHS (see Figs. 10.1 and 10.2):

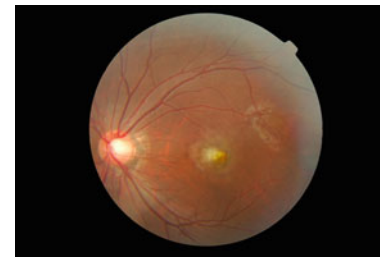

Fig. 10.1 Color fundus photograph of a patient with peripapillary atrophy and macular choroidal neovascular membrane secondary to POHS. There was no vitritis on physical exam

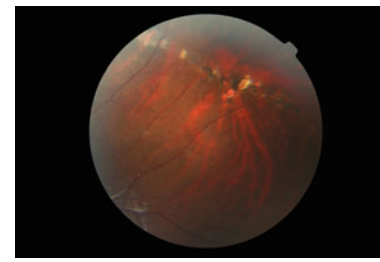

Fig. 10.2 Peripheral retina of patient in Fig. 10.1 demonstrating chorioretinal scarring

1. Multiple white atrophic chorioretinal scars (also known as histo spots)
2. Peripapillary atrophy
3. Absence of vitritis

Histo spots are discrete, focal; atrophic choroidal scars found in the posterior pole and the peripheral retina. They appear to be "punched out" of the inner choroid with central pigmentation, ring of pigmentation, or diffuse pigmentation. They may indicate former areas of subclinical CNV that have regressed spontaneously. Linear streaks that are parallel to the ora serrata may be found in around 5 % of patients [21]. These streaks may simply be the coalescence of small linear histo spots. The scars may remain stable but in some patients, they have been documented to grow in size or number [22, 23].

Peripapillary atrophy is more commonly associated with macular scars. About a third of patients with peripheral histo spots will have peripapillary chorioretinal scars versus over two-thirds of patients with macular scarring. The peripapillary atrophy may represent a ring of granulomas that formed during the active stage of the disease [20, 24].

POHS may only be diagnosed in the absence of vitreous cells or anterior inflammation. Pigmented cells should not be confused with inflammatory cells. The lack of cells may be attributed to patients presenting after the active inflammatory stage has passed. Another theory is that since POHS is mainly a choriodopathy, the cells do not reach the vitreous.

These classic POHS findings may or may not be associated with CNV. Active disciform lesions may look like a green-gray subretinal lacy discoloration with surrounding pigment, usually in the macula. It may be related to chorioretinal scars that have a break in Bruch's membrane. CNV usually occurs at the edge of an old scar. A scar in the macula or peripapillary region appears more predisposed to progressing to CNV. However, CNV can also form in the macula where there was previously no scar. If advanced, CNV appears as a white disciform scar with fibrovascular tissue. Rarely, as with age-related macular degeneration, CNV may result in vitreous hemorrhage due to a break in the retina [25].

Diagnostic Procedures

POHS is usually a clinical diagnosis, but fluorescein angiography (FA) can assist in the diagnosis. In areas of chorioretinal atrophy, staining and window defects versus late leakage can be seen with CNV. Defects in the retinal pigment epithelium and patchy loss of the choriocapillaris can be seen. Krill et al. described histo lesions as being hypofluorescent initially but then acquiring a more hyperfluorescent appearance late in the disease [26]. FA can be useful in locating areas of neovascularization if laser treatment is employed for CNV.

The histoplasmin skin antigen test can help determine if the patient has been exposed to *H. capsulatum.* However, since up to two-thirds of patients in endemic areas have a positive skin test, this testing is not routinely performed if the clinical findings are classic.

Differential Diagnosis

Diseases causing granulomas such as tuberculosis, coccidiomycosis, cryptococcosis, and sarcoidosis, should be considered. Careful examination for vitreous inflammation can help distinguish POHS from these other diseases.

Other causes of chorioretinitis must also be considered, including multifocal chorioretinitis, serpiginous choroiditis, birdshot chorioretinopathy, multiple evanescent white dot syndrome, acute multifocal placoid pigment epitheliopathy, toxoplasmosis, toxocariasis, rubella, Vogt-Koyanagi-Harada syndrome, and Behçet syndrome. Most commonly, multifocal choroiditis may be confused with POHS, but again, the absence of vitreous cells in POHS is the key distinguishing feature [27]. PIC lesions may also appear very similar to the chorioretinal scars of POHS, but the PIC scars tend to be small and confined to the posterior pole [28].

Management

Indications

POHS without CNV is monitored with biomicroscopy and the Amsler grid. Since there is no solid evidence of the organism being present in the eye, antifungal treatment such as amphotericin B is not beneficial [29, 30]. When CNV develops in the macula, it is treated similarly as age-related macular degeneration. Peripapillary CNV may be monitored unless it causes prolonged serous or hemorrhagic detachment close to the fovea.

Laser Therapy

The Macular Photocoagulation Study (MPS) evaluated laser photocoagulation for extrafoveal (>200 μm from the center of the foveal avascular zone), juxtafoveal (1–200 μm from the center of the foveal avascular zone), and peripapillary CNV. The MPS found that untreated eyes had 3.6 times the risk of laser treated eyes of losing six or more lines of visual acuity. However, the major complication of this treatment was a permanent scotoma from the laser, limiting its use for subfoveal lesions. Furthermore, 26 % of extrafoveal CNV and 33 % of juxtafoveal CNV recurred at the border of the treatment scar [31, 32].

The Verteporfin for Ocular Histoplasmosis Study examined the use of photodynamic therapy. This looked at photodynamic therapy for subfoveal CNV. The study found that 45 % of patients experienced improved vision, 18 % lost vision, and 9 % of patients suffered severe vision loss at the 2-year follow up. No serious adverse side effects were reported [33, 34].

Surgery

Submacular surgery has been explored for the treatment of subfoveal CNV. Thomas and Kaplan first described techniques to remove subfoveal CNV in POHS patients [35]. Using a small retinotomy with the creation of a neurosensory retinal detachment allowed access to the fibrovascular membrane. There was a significant improvement in their patients without recurrence of CNV. However, these dramatic findings were not duplicated by subsequent studies that employed a larger population and longer follow up. It has been speculated that surgery to remove membranes in POHS patients is more successful than surgery in patients with age-related macular degeneration, because POHS CNV lesions are not as deeply located. The retinal pigment epithelium may also recover and proliferate better given this more superficial location and the fact that most patients are younger than those with age-related macular degeneration. However, as with any vitreoretinal surgery, the risks include cataract, retinal detachment, and lesion recurrence [36–38].

Steroids

In 1977, Schlaegel et al. recommended high dose oral corticosteroids for acute exacerbations of macular CNV. With the advent of anti-VEGF treatment, this practice is not commonly used [39].

Anti-VEGF Agents

Most recently, anti-vascular endothelial growth factor (anti-VEGF) agents such as bevacizumab and ranibizumab have been used in patients with POHS given the success of these treatments for age-related macular degeneration. A recent retrospective study of POHS-associated CNV found that the average visual acuity improved from 20/53 to 20/26 in 54 eyes treated over a 26-month period. The average number of injections was 4.5 over one year [40]. Anti-VEGF agents are now considered first line treatment for patients with POHS and CNV. Risks of anti-VEGF injections include endophthalmitis, subconjunctival hemorrhage, cataract formation, retinal tears, and increased intraocular pressure [41].

Prognosis

Patient with histo spots in one eye have an 8–24 % chance of developing CNV in the fellow eye over 3 years [31, 32]. Complications of CNV include disciform scarring, resulting in loss of central vision. The visual acuity has been

reported to be about 20/200 in about half of patients untreated. Spontaneous recovery has been reported but may have been secondary to the development of eccentric vision [42]. However, when CNV is identified early, anti-VEGF treatments can maintain good visual acuity. Patients should be counseled appropriately on their risk of developing macular disease [43].

Prevention

There is no current primary prevention. Patients with clinical signs of POHS should be screened for CNV with routine dilated fundoscopic exams. Patients should monitor disease activity at home with the Amsler grid.

Conclusion

POHS is a choroidopathy, typically characterized by atrophic chorioretinal scars, peripapillary atrophy, and the absence of vitritis. The ocular manifestations are presumably secondary to a complex and poorly defined interaction between the fungal organism *H. capsulatum* and the host immune response. Patients without CNV require monitoring without treatment. When CNV develops in the macula, intraocular anti-VEGF agents are the preferred option for therapy.

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