Ocular histoplasmosis syndrome (OHS) is a common, mostly subclinical, multifocal chorioretinal disorder characterized by peripapillary atrophy (PPA), chorioretinal scars, and possible development of choroidal neovascularization (CNV). The disease has been attributed to an accidental infection with a dimorphic fungus called Histoplasma capsulatum.

1. Introduction

Ocular histoplasmosis syndrome (OHS) is a common, mostly subclinical, multifocal chorioretinal disorder characterized by peripapillary atrophy (PPA), chorioretinal scars, and possible development of choroidal neovascularization (CNV). The disease has been attributed to an accidental infection with a dimorphic fungus called Histoplasma capsulatum. Samuel Darling discovered this fungus in 1905 in the Panama Canal Zone while examining spleen and liver smears from patients suspected of having kala-azar disease. A greater accuracy in the diagnosis of chorioretinal disease and the treatment of CNVs has been achieved by advanced high-resolution retinal imaging technology and the advent of anti-vascular endothelial growth factor (anti-VEGF) therapy.
1.1. **History**

Since the early 1940s, many scholars, including Reid, Woods and Wahlen, and Schlaegel, have described the constitutional and ocular characteristics of the disease. In the 1980s, Gass compiled all previously described clinical findings in OHS in his landmark macular atlas and proposed a potential pathogenesis. Perhaps his most notable contribution was his illustrated hypothesis concerning CNV formation and secondary development of a disciform scar. He also clarified the distinction between OHS and other simulating lesions.

1.2. **Demographics**

1.2.1. **Age range**

Patients are typically diagnosed between 20 and 50 years of age (range: 10–81). The primary infection likely occurs many years prior to the development of symptoms, and therefore peripheral chorioretinal scars and PPA are incidental findings in young patients evaluated during routine eye exams.

1.2.2. **Sex and race**

Males and females are affected equally. In terms of ethnicity, several reports have described that OHS signs and symptoms are more common among white patients than black or Hispanic patients. When comparing the prevalence of histoplasmin skin test reactions between white and black patients, however, no significant difference was found, suggesting that sensitization occurs equally in both groups.

1.3. **Epidemiology**

1.3.1. **Geographic distribution**

Histoplasmosis is the most endemic mycosis in the world. In the United States, the "histo belt" is defined by a triangle with apices in Eastern Nebraska, Central Ohio, and Southwestern Mississippi, a region that is commonly referred to as the Mississippi and Ohio river valleys. Tennessee has the highest incidence of histoplasmosis infection in the United States. Despite the worldwide distribution of the fungus, OHS has been reported in only a few countries outside the United States, including Mexico, India, the United Kingdom, and the Netherlands. The absence of OHS in many countries may call the etiology into question or may represent a lack of documentation.

1.3.2. **Environmental exposure**

*H. capsulatum* exhibits two distinct morphologies depending on the environmental conditions: the mycelial ("filamentous" or "mold") form found in the soil and the yeast or spherule form found inside the host. The primary route of infection is inhalation of infectious spores or conidia. The dampness of the environment is highly correlated with *Histoplasma* skin test sensitivity and corresponds to places with reported concentrations of histoplasmosis infections, such as excavations, old buildings, bird habitats, or caves inhabited by bats. After initial exposure to the fungus, mild flu-like symptoms may develop. Following this primary infection, most patients will develop asymptomatic calcified pulmonary nodules and positive histoplasmin skin reactions.

1.3.3. **Incidence and prevalence**

The real incidence of OHS is largely unknown. The reported prevalence of atrophic scars ranges between 1.6% to 5.3%. In patients with known disease, some have estimated the incidence of neovascular lesions in the fellow eye to be up to 12% per year.

Patients are at risk for marked visual disturbance, particularly after developing CNV or a subsequent macular scar. According to Feman et al in 1982, OHS is responsible for 2.8% of visual impairments among Tennessee’s applicants for services for the blind.

1.4. **Clinical presentation**

1.4.1. **Classic triad**

OHS is a clinical diagnosis with distinctive posterior segment findings in the absence of vitritis or anterior segment inflammation. It is generally agreed that one or both eyes should manifest at least two of the classic triad components (Fig. 1).

1. Chorioretinal peripapillary atrophy (PPA)
2. Chorioretinal scars in the macula and mid-periphery ("histo spots" or "punched out" lesions)
3. Choroidal neovascularization (CNV) or corresponding sequelae, such as disciform scars

Patients may present with metamorphopsia, decreased vision, or paracentral scotomas from possible active CNV. PPA and extrafoveal chorioretinal scars do not produce visual symptoms. Characteristic peripapillary atrophy is circumferential, with atrophy adjacent to hyperpigmentation (Figs. 1 and 2).

1.4.2. **Acute manifestations**

Descriptions of the acute manifestations of OHS are scarce; this is most likely the result of the lack of visual symptoms during primary infection. The closest description is the presence of new, white-creamy spots not previously recognized on fundus examination that appear a few days or weeks following the initial infection. This may be an incidental finding on asymptomatic patients and may be accompanied by mild respiratory symptoms.

Katz et al described an acute presentation of OHS in two immunocompetent brothers who lived in an endemic area. After being exposed to goose guano, they developed a cough, low-grade fever, and general malaise of 3 weeks’ durations with x-ray findings consistent with pneumonitis. Seven weeks following the initial illness, an ophthalmic evaluation revealed a best corrected visual acuity of 20/20 OU in both siblings, no signs of vitritis, but “single, distinct, round, creamy-white, deep” lesions in both brothers, located in the temporal macula and peripapillary areas.

A primate model also demonstrated the clinical, morphological, and histopathologic appearance of acute OHS as early as 3–4 days after the injection of live *H. capsulatum* organisms into the internal carotid artery. A subtle motting of...
the fundus was noted in the ipsilateral eye and further confirmed by fluorescein angiography. These foci developed into more clinically distinct round or oval, focal, poorly circumscribed yellowish spots mainly distributed in the posterior pole 5–7 days after the inoculation of the organisms.

1.4.3. Late manifestations

OHS’s natural history indicates that the initial discrete, yellowish chorioretinal lesions eventually become pigmented and enlarged and become abundantly distributed in the midperiphery and posterior pole. Untreated CNVs evolve into large disciform scars, usually in the subfoveal region, resulting in decreased vision, typically 20/200 or worse.71,129,158

2. Basic science

2.1. Pathogenesis

The pathogenesis of OHS has been debated since its original description. A direct cause–effect relationship between H. capsulatum and the clinical syndrome has been tenuous since early reports, which has led to the terminology presumed ocular histoplasmosis syndrome (POHS). Evidence supporting the relationship between the organism and ocular presentation include epidemiological data from endemic areas, the high proportion of positive histoplasmin skin reaction in patients living in endemic areas,7,34,35,39,42,164 animal experiments that reproduced the ocular signs of OHS,63,140,143,144,161 the presence of H. capsulatum on pathologic sections of enucleated eyes,50,70,119,120 and the isolation of H. capsulatum DNA in the peripheral blood and chorioretinal scars of patients with known OHS.56,149

Evidence refuting a direct relationship between H. capsulatum and OHS is based on the presence of clinical findings of OHS in non-endemic areas with anergy to histoplasmin skin test,4,11,16,107,150 a lack of fulfillment of Koch’s postulates,14,147 few if any patients with systemic histoplasmosis developing the ocular syndrome,4,147 the absence of therapeutic response to amphotericin B,46,47 and minimal or no therapeutic response with steroids.7,106

Fig. 2 – Clinical findings of ocular histoplasmosis syndrome. Color fundus photography revealing clear media, absence of vitritis, and bilateral, asymmetric peripapillary atrophy with patchy areas of interrupted pigmentation around the optic nerve. A small nonpigmented chorioretinal scar is observed directly inferior to the optic nerve (left); the left eye reveals a subfoveal, subretinal pigment epithelium choroidal neovascularization, characteristic histo-type peripapillary atrophy, and two discrete chorioretinal scars (right).
as Epstein-Barr\textsuperscript{11} or other systemic mycosis (Coccidioidomycosis, Paracoccidioidomycosis, and Blastomycosis) that may have crossed-immunity, thus causing the syndrome.\textsuperscript{13,97}

Another proposal is the parainfectious hypothesis, where OHS belongs to a spectrum of disorders with final common chorioretinal manifestations triggered by \textit{H. capsulatum} or any organism with similar antigens. It may manifest as OHS, punctate inner choroidopathy, or multifocal choroiditis and panuveitis depending on variability of the host’s immune system and the virulence of the organism.\textsuperscript{7,150,161}

### 2.1. Choroidal seeding theory

The most accepted theory suggests that once spores are inhaled, they replicate in the alveolar macrophages, inducing fungemia and choroidal seeding through hematogenous dissemination.\textsuperscript{37,42,45,57,97,140} On histopathology, localized lymphocytic infiltration is found on chorioretinal scars or histo spots. Some reports have constantly demonstrated the disruption of Bruch membrane and the retinal pigment epithelium (RPE). In fundus autofluorescence, OHS lesions correspond to an area of hypoautofluorescence, supporting the histopathologic findings. With over 30 years of experience with patients in the Mississippi River Valley, we have anecdotally noticed a high prevalence of OHS-type lesions in patients who spend increased time outdoors. Therefore, we speculate that repeated exposure may lead to an increased number of OHS lesions over time, and may increase the incidence of macular lesions and CNV risk.

### 2.1.1. Choroidal seeding theory

Patients who develop CNV are at significant risk of developing functional impairment from macular atrophy and scarring. The Macular Photocoagulation Study Group (MPS) found that 9\% of fellow eyes originally free from neovascular maculopathy developed CNV, for an annual incidence rate of 1.8\%.\textsuperscript{83} In addition, the presence of macular OHS lesions was an independent risk factor for the development of CNV. Patients with macular OHS lesions in the fellow eye at baseline were three times more likely to develop CNV at 5 years than those who did not present with macular OHS lesions. The notion of macular OHS lesions as a risk factor for CNV was previously observed by others during the 1970s.\textsuperscript{54,76,139} Savelson et al followed the course of the disease in patients with the classic triad in one eye and punched-out chorioretinal scars in the macular area of the fellow eye.\textsuperscript{125} They found an incidence of 24\% of hemorrhagic or serous sequelae corresponding to the activation of pre-existing, asymptomatic, macular atrophic scars. The interval from the first observation to activation ranged from 13 to 59 months. Smith reported a greater interval, from 4 to 102 months.\textsuperscript{139} Gutman\textsuperscript{51} observed that 21\% of fellow eyes developed an active choroidal lesion from pre-existing atrophic scars after a year or more of follow-up.

### 2.2. Relationship between ocular disease and systemic exposure

#### 2.2.1. Histoplasmin skin test

The introduction of the histoplasmin skin test in 1941 transformed the perception of histoplasmosis from a rare, fatal disease into a common, subclinical infection.\textsuperscript{162} The histoplasmin antigen is prepared from \textit{H. capsulatum} proteins. Using the Mantoux technique, 0.1 mL of 1:100 diluted histoplasmin is injected intradermally in the volar surface of the left forearm. The test is read 48 hours later, and the largest diameter of induration is measured. A positive reaction is defined by 2 mm or more of central induration with erythema.\textsuperscript{42,141,162} This indicates that a patient has been exposed to the fungus, but does not indicate active disease. The prevalence of positive histoplasmin skin test is as high as 92\% in endemic areas (specifically Shelby County, TN) or as low as zero in non-endemic areas (Richland County, SC).\textsuperscript{34} Other reports have shown that approximately 60\% of the population living in endemic areas are exposed to the fungus and react positively to a histoplasmin skin antigen challenge.\textsuperscript{7,35,39,42,164} A study in Williamson County, TN, demonstrated a progressive increase in positive histoplasmin skin test reactions, starting with 25\% in children under 1 year of age to 87\% positivity in those 10–14 years old.\textsuperscript{164}

Currently, the histoplasmin skin test is not routinely performed on OHS patients. Exacerbation of OHS with increased hemorrhaging from previous macular CNVs or atrophic scars may follow the intradermal injection of histoplasmin.\textsuperscript{73} In addition, it is not a specific test for histoplasmosis because it may cross-react with other types of fungi, especially Blastomyces \textit{dermatitidis}\textsuperscript{162} and \textit{Coccidioides immitis}.\textsuperscript{23} Another disadvantage is the stimulation of antibody production, with a positive complement-fixing antibodies test after the histoplasmin skin challenge.\textsuperscript{68,144}

#### 2.2.2. Histopathologic findings

Pathologic analyses of enucleated eyes have found \textit{H. capsulatum} in the endothelial cells of the choroid\textsuperscript{131} and focal areas of the retina.\textsuperscript{50,119} Positive immunohistopathological stains for Histoplasma antigens were found in an eye with POHS at sites of lymphocytic inflammation.\textsuperscript{61}

Several authors found the presence of \textit{H. capsulatum} in histopathologic sections of choroidal lesions in patients with disseminated histoplasmosis.\textsuperscript{58,72,81,131,132} Klintworth described a case of an immunocompromised young man with disseminated histoplasmosis and “few, small, white drusenoid bodies” in the macular area of his left eye.\textsuperscript{72} Upon autopsy, these choroidal lesions had focal accumulation of macrophages and mononuclear cells with a disrupted RPE. Sabouraud cultures were positive for \textit{H. capsulatum}, and the organism was found on choroidal stained tissue.

Given that OHS is a different clinical entity from disseminated histoplasmosis, a number of studies have been performed using enucleated eyes with OHS.\textsuperscript{61,70,97,119,120} Ryan described five cases of eyes clinically diagnosed with OHS, but enucleated because of a malignant melanoma.\textsuperscript{120} On histopathology, there was choroidal, RPE, and outer retina layer atrophy. He found \textit{H. capsulatum} in only one case using a Gomori methenamine silver stain. Irvine also described the findings from an eye with OHS that was later enucleated because of a malignant choroidal melanoma. On light microscopy, the PPA, macular chorioretinal scar, and focal chorioretinal lesions in the midperiphery showed evidence of the destruction of the RPE with the loss of outer retinal layers. The subjacent choroid and peripheral chorioretinal scars contained inflammatory cells, predominantly lymphocytes.
Subretinal neovascularization was found in some of these lesions. No organism was identified via light or electron microscopy, although immunohistopathologic stains tested positive for *Histoplasma* antigens at sites of lymphocytic infiltration.61

Meredith et al described three clinicopathologic cases of clinically typical OHS. Histopathologic analysis revealed Bruch membrane disruption, fibrovascular nodules between Bruch membrane and the neurosensory retina, and lymphocytic infiltration on peripheral chorioretinal scars. Special staining tested negative for *Histoplasma* antigen.97

Roth demonstrated the presence of *H. capsulatum* in histopathologic sections of a patient with bilateral macular disciform scars and peripheral chorioretinal lesions.119 Histopathologic findings were consistent with Bruch membrane and RPE disruption, the disruption of outer retinal layers by a subjacent fibrovascular subretinal mass in the macular lesions, and moderate lymphocyte infiltration in the choroid. The diagnosis of OHS was made post mortem, with gross anatomic sections fulfilling all OHS criteria. Although the patient never lived in an endemic area, *H. capsulatum* organisms were found in granulomatous lesions in the lungs and both eyes.

Khalil reported a case of a patient clinically diagnosed with OHS who required enucleation of his right eye because of a choroidal malignant melanoma. Histopathology and electron microscopy of granulomatous lesions demonstrated the presence of dead *Histoplasma* organisms.70 This finding supports the idea of OHS as a parainfectious disorder.

### 2.2.3. *H. capsulatum* DNA in different tissues

One of the most compelling pieces of evidence is the *H. capsulatum* DNA found in the peripheral blood of a patient with subretinal CNV secondary to OHS61 and in an enucleated eye of a patient with bilateral POHS and a positive histoplasmin skin test.147 Spencer et al identified products of *H. capsulatum* DNA through the polymerase chain reaction amplification technique. They retrieved archived microslides prepared in 1975 by Irvine et al.147 Samples taken from the macular and midperipheral retinal lesions of the left eye were compatible with the positive control, but not with the negative control.149 Hernandez et al reported a case of an immunocompetent male who presented with general malaise, fever, cervical lymphadenopathy and sudden visual loss in his right eye. A type 2 CNV was noted on fluorescein angiography (FA) and optical coherence tomography (OCT). Polymerase chain reaction amplification analysis from peripheral blood was positive for a *Histoplasma*-specific protein and revealed 97% similarity with the reference sequence.56

### 2.2.4. Animal experiments

In 1942, Reid isolated *H. capsulatum* from the peripheral blood of a patient dying from disseminated histoplasmosis. He successfully reproduced the systemic disease in guinea pigs, but provided no details regarding the ocular pathology of these animals.116 Inoculation of *H. capsulatum* produced a granulomatous uveitis in rabbits,29,142,161 rats,104 pigeons,131,141 and dogs.122 Four weeks following the intravenous inoculation of *H. capsulatum* spores in rabbits, typical peripheral chorioretinal lesions developed from which organisms were recovered.162 Interestingly, no organisms were identified in the contralateral eyes of the same animals 8 weeks following inoculation. The authors suggested that the “emergence of immunity” at 2 months precluded the recovery of the organism.

Smith and colleagues pioneered experimental primate OHS models using different inoculation routes. In 1964, they injected the yeast-phase of *Histoplasma* into the anterior chamber of monkeys, producing a granulomatous iridocyclitis with later recovery of the fungi. The posterior pole was not affected in this study. The first experimentally produced retinal and choroidal lesions occurred 2 weeks after an intravitreal injection of *H. capsulatum* in rabbits’ and monkeys’ eyes. The histopathology of these eyes demonstrated the presence of the fungi.143,144

Smith and colleagues also considered different doses of *H. capsulatum* in their experiments. Using low doses of the yeast-phase, the eyes remained clear without any signs of infection even 6 weeks following the inoculation, but some animals became histoplasmin positive. After this observation, the authors hypothesized that humans rarely develop a progressive granulomatous uveitis in OHS because the fungi enter the ocular circulation in minimal concentrations.144

In 1978, Smith et al simulated the hematogenous route of infection, injecting live *H. capsulatum* into the common or internal carotid artery of monkeys.140 All of the animals had a negative histoplasmin skin test prior to inoculation. Most monkeys developed an ipsilateral chorioretinitis either with the common or the internal carotid artery approach. The severity of the disease was intimately related to the size of the inoculum. The internal carotid artery group experienced less variability in the results. Most animals converted to a positive histoplasmin skin test. As early as 3 days following inoculation, subtle mottling was observed on the posterior pole. At day 6, a serous retinal detachment was observed on the peripapillary area of one animal that improved spontaneously over time. Most lesions remained recognizable even at day 30. On histopathology, *H. capsulatum* was within the lesions, there was lymphocytic infiltration of the choroid, and some specimens showed disruption of Bruch membrane and the RPE. Some of these monkeys were followed for a 3-year period in order to study the resolution of the acute choroiditis. By 6 weeks following the inoculation of the internal carotid artery, there was no histopathologic evidence of the presence of *H. capsulatum* in any eye.146 Four types of lesions were recognized during this phase: atrophic scars, RPE window defects, subclinical infections identified only by FA, and disappearing lesions with normal fundus and FA. They failed to reproduce a macular CNV or reactivation of inactive scars. The spontaneous resolution of many of the lesions suggested the ability of the host’s immune system to overcome the infection.145 A year later, Jester and Smith successfully reproduced a subretinal neovascularization in a primate following the inoculation of the yeast-phase of *H. capsulatum* in the internal carotid artery.63

A more recent report described the inflammatory cells within the choroidal infiltrates in monkeys’ eyes using anti-human monoclonal antibodies.155 CD4 and CD8 T-lymphocytes were the predominant cell types observed in both acute (<65 days) and chronic (1–7 years) lesions. Chronic lesions
had fewer inflammatory cells and were further divided into lesions with and without B-cell foci. Those lesions with B-cell foci had a higher proportion of B-cell lymphocytes compared to acute lesions. Several hypotheses were offered for these findings, starting with the possibility that not all chronic lesions have the same immune potential for reactivation.

2.2.5. Histoplasma capsulatum strains and virulence

Three varieties of *H. capsulatum* have been recognized according to their clinical manifestations and geographic distribution: *H. capsulatum var. capsulatum* (human pathogen found in the American continent), var. duboisii (human pathogen found in Africa), and var. farciminosum (a European horse pathogen). Kasuga and colleagues studied the phylogenetic relationship of the three varieties among individuals from six continents and identified eight clades through DNA analysis: (i) North American class 1 clade; (ii) North American class 2 clade; (iii) Latin American group A clade; (iv) Latin American group B clade; (v) Australian clade; (vi) Netherlands clade; (vii) Eurasian clade and (viii) African clade. They stated that seven of the eight clades represented genetically isolated groups that should be considered independent phylogenetic species instead of varieties. Two of the most studied strains, the NAm2 strain G217 B (North American) and G186 A (Latin American) revealed genetic and virulence differences that may lead to distinct pathogenic mechanisms. Known virulence factors include the presence of protein Cbp1, cell wall z-glucan, Yps3 factor, and SID1 gene.

2.3. Genetics

Multiple reports found an association between OHS and human leukocyte antigen (HLA) subtypes (DRw2, DR15 DQ6, B7), suggesting a genetic susceptibility or predisposition for the development of OHS. Up to 78% of patients with clinical OHS and macular disciform scars in at least one eye have positive HLA-B7. In contrast, patients with only atrophic scars did not show a high frequency of HLA-DR15 and HLA-DQ6 are associated with the development of CNV in OHS. Dabil et al found that HLA-DR15 and HLA-DQ6 are associated with the development of CNV in OHS. Recently, Wilkes et al studied the prevalence of the risk alleles known to cause CNV in age-related macular degeneration in patients with OHS. They failed to demonstrate a correlation between the risk alleles and the occurrence of CNV in OHS.

3. Morphology and clinical spectrum

3.1. Ophthalmoscopy and fundus photography

3.1.1. Anterior segment findings

OHS is characterized by the absence of inflammation in the anterior segment and vitreous.

3.1.2. Posterior segment findings

The clinical diagnosis of OHS is based on the ophthalmoscopic examination of the posterior segment, looking for PPA, chorioretinal scars, and CNV (disciform scar) in the absence of vitritis. None of these alone are sufficient, and it is generally agreed that at least two must be observed in order to make the diagnosis. The presence of peripheral chorioretinal scars increases the level of clinical suspicion, especially if the patient lives in an endemic area. Up to 70% of patients have bilateral PPA, 15% unilateral, and 15% have no PPA. The presence of typical, ring-like, pigmented PPA may assist in the diagnosis (Figs. 1–3).

Peripheral chorioretinal scars or histo spots are characterized by their round or oval shape, random distribution in the periphery or midperiphery, small size (ranges between 0.1–0.5 disk diameter), diffuse borders, and variable pigmentation. They can easily be distinguished on dilated fundus examination (DFE) and fundus photography in their chronic phase, when they have a characteristic pigmentation (Fig. 1). Acute lesions have a gray-white appearance, are smaller in size, and will not be easily distinguished on DFE or color fundus photograph (Figs. 2 and 3). In these cases, fundus autofluorescence and fluorescein angiography are particularly helpful in detection. In 1975, Schlaegel reported the natural history of 467 OHS lesions located in the disk and macular area of 66 patients. He found a mean of 5.5 lesions per eye (range: 1–48). He also observed that each lesion behaved differently: 46% increased in size, 45% became smaller or disappeared, and 8% remained unchanged. Smaller spots had a higher tendency to disappear, but even after vanishing, they could return. He identified 121 new spots that appeared after a mean period of 5 years.

Without treatment, CNVs will progress to a fibrous scar or rarely exhibit spontaneous regression. The formation of neovascular membranes implies the disruption of Bruch’s membrane either from a chorioretinal scar or a previous disciform lesion. Linear streaks of chorioretinal scars can be found in 5% of patients with OHS. They are usually found in the equatorial region oriented parallel to the ora serrata and can have variable length, width, and pigmentation.

3.2. Angiography

3.2.1. Fluorescein angiography

CNVs secondary to OHS manifest the same characteristics as any other choroidal neovascularization. In the early arterial phase, the new-abnormal choroidal vessels are rapidly filled. On successive FA phases, there is leakage of fluorescein dye from the abnormal vessels that increases in intensity with expanding borders. PPA and chorioretinal scars exhibit a window defect pattern of hyperfluorescence and progressive scleral staining. (Fig. 4)

3.2.2. Indocyanine green angiography

Indocyanine green angiography (ICG) supplements the FA findings, especially in patients with sub-RPE lesions, also known as “occult” CNVs. Increased hyperfluorescence is visible from new, disorganized choriocapillaris on early ICG.
3.2.3. Optical coherence tomography
Cross-sectional (b-scan) spectral-domain optical coherence tomography (SD-OCT) provides detailed information regarding the localization and extent of CNV (Fig. 5). It is also an excellent tool to monitor disease activity. On SD-OCT, macular OHS lesions or histo spots are distinguished by a focal area of outer retinal atrophy, giving the appearance of a “punched out” scar (Fig. 6). The normal hyper-reflective bands of the outer retina look disorganized because of the loss of their intrinsic reflectance compared with the surrounding normal retina. This phenomenon is also observed in patients with PPA.

On infrared imaging, PPA is characterized by a hyper-reflective irregular halo surrounding the optic nerve. Disciform scars and macular histo spots also present as hyper-reflective irregular areas (Fig. 6, bottom left). Fundus autofluorescence is also a useful imaging modality because of its higher sensitivity in detecting small, nonpigmented macular chorioretinal scars than color fundus photography (Fig. 3). These lesions have a round, hypo-autofluorescent appearance.

3.3. Variants and differential diagnoses
OHS shares many similarities with the spectrum of conditions called “white dot syndromes”. These include multifocal chorioiditis with panuveitis (MCP), punctate inner choroidopathy (PIC), multiple evanescent white-dot syndrome (MEWDS), acute posterior multifocal plaid pigment epitheliopathy, birdshot retinochoroidopathy, diffuse subretinal fibrosis, and serpiginous choroidopathy. OHS should also be differentiated from other causes of CNV, such as idiopathic CNV, choroidal rupture with CNV, myopic CNV, and exudative age-related macular degeneration (AMD). Other inflammatory and infectious diseases such as sarcoidosis and toxoplasmosis may

Fig. 3 – Comparison of color fundus photography and fundus autofluorescence for the detection of chorioretinal scars in ocular histoplasmosis syndrome. Color fundus photograph shows one chorioretinal scar or histo spot superior to the fovea and another two of these lesions inferonasal to the fovea along the inferior arcade (left); fundus autofluorescence reveals the presence of several chorioretinal scars that were not easily distinguished in color photography, especially along the superior arcade and the area superior to the optic nerve (right). These hypoautofluorescent lesions correspond to areas of absent RPE present in chorioretinal scars secondary to ocular histoplasmosis.

Fig. 4 – Fluorescein angiography findings in ocular histoplasmosis syndrome. Color fundus photograph reveals patchy peripapillary atrophy, one discrete white chorioretinal scar inferotemporal to the fovea, and a superotemporal, subretinal choroidal neovascularization with subretinal hemorrhage and fluid extending to the foveola (left); fluorescein angiography shows the blockage of dye corresponding to the area of hemorrhage, leakage in the area corresponding to the choroidal neovascularization, and pooling in the inferonasal lesion, identified as a small chorioretinal scar (right).
also mimic OHS. In the following sections, we describe some entities that may be difficult to differentiate from OHS.

3.3.1. Multifocal choroiditis with panuveitis
Originally described by Nozik and Dorsch in 1973, and further analyzed by Dreyer and Gass, MCP is a chorioretinopathy characterized by punched-out scars or gray-yellowish spots in association with anterior uveitis and/or vitritis during active disease. The lesions have the potential to develop CNV and peripapillary scars. MCP is more common among women, in contrast with OHS, which has no sex predilection. If the patient presents on the active phase of the disease, a careful examination seeking anterior chamber cells and/or vitreous cells may help distinguish this entity. MCP patients frequently have typical myopic PPA in contrast to the circumferential OHS PPA. Considering that the three elements of the classic triad of OHS may be present on MCP, if no anterior chamber cells or vitreous cells are present, a definitive diagnosis may be challenging, especially if the patient lives in an endemic area for OHS and presents during the inactive phase of this uveitic process. One difference is that MCP and PIC patients usually lack typical OHS PPA. Generally speaking, MCP chorioretinal scars have a larger diameter, followed by medium-size OHS lesions and the small PIC lesions. It is not recommended to use the scar size as a distinguishing feature, however, because the size range of the chorioretinal scars can overlap between the three conditions. In 2001, a study intended to find any imaging difference between MCP or OHS. Two masked observers classified the fundus color photographs and FA images of 50 eyes as MCP, OHS, or indeterminate. Half of the eyes had known OHS and the other half, MCP. Observers A and B had a crude accuracy of 79% and 82%, respectively. They both classified 26 eyes correctly and were more sensitive to MCP than to OHS. FA images did not improve their diagnostic precision. That report provided insight into how similar these diseases can appear and how easily they can be confused even by experienced observers.

3.3.2. Punctate inner choroidopathy
First described by Watzke, PIC is a multifocal inflammatory choroidopathy characterized by small, yellow-white spots in the outer retina or inner choroid without anterior uveitis. It is more common among young myopic females, with 40% of patients developing CNV. The lesions become pigmented over time, making them indistinguishable from OHS lesions. A recent study used multimodality imaging to analyze the structural differences in eyes diagnosed with MCP or PIC. Seven of 22 patients had a discordant classification of their two eyes, suggesting that PIC is a subset of MCP. Diagnosing PIC becomes more difficult in a young myopic female living in an endemic area for histoplasmosis.

3.3.3. Multiple evanescent white-dot syndrome
MEWDS is an acute inflammatory chorioretinopathy characterized by multiple small, gray-white patches at the level of the outer retina or RPE. Other distinctive features are the presence of vitreous cells, blurring disk margins, and macular orange dots. It is more common among young females and it spontaneously resolves after 6–10 weeks. FA, ICG angiography, and electroretinography are useful tools to diagnose MEWDS. ICG angiography typically discloses greater amounts of lesions than FA or ophthalmoscopy.

3.3.4. Idiopathic choroidal neovascularization
Idiopathic CNV, the development of abnormal choroidal vessels, particularly in young patients, without having a definite
etiology, is considered a diagnosis of exclusion after discarding other CNV-developing conditions such as exudative AMD, pathologic myopia, OHS, and angioid streaks. Idiopathic CNV should not present with peripheral or macular chorioretinal scars or PPA.

3.3.5. Choroidal rupture with choroidal neovascularization
Choroidal rupture occurs as a result of blunt ocular trauma with the disruption of the choriocapillaris and Bruch membrane. As a result, subretinal and sub-RPE hemorrhages are common findings associated with whitish, crescent-shaped lesions concentric to the optic disk. Secondary CNV can occur at any time during the follow-up period, usually at the edge of the rupture. Peripheral chorioretinal scars and PPA are not present.

3.3.6. Myopic degeneration
Progressive elongation of the eye observed in patients with more than six diopters of myopia will produce thinning of the RPE and choroid. There is a higher risk for spontaneous breaks in Bruch membrane, known as lacquer cracks, which are associated with subretinal hemorrhage with or without the development of CNV. Other typical findings include the “myopic crescent,” usually in the temporal aspect of the disk, and diffuse, extensive areas of chorioretinal atrophy located on the peripheral retina. If the myopic crescent is large enough to involve the entire circumference of the disk, it can simulate the PPA observed in OHS, although circumferential pigmentation is usually absent. Finally, considering the intrinsic potential of degenerative myopia to develop CNV and peripheral chorioretinal atrophy, OHS might be confused with pathologic myopia. Both diseases can be present in an individual as they are not mutually exclusive.

3.3.7. Neovascular age-related macular degeneration
AMD is a common degenerative condition involving the macular area of patients 50 years old and older. Exudative AMD implies the development of CNV through defects in Bruch’s membrane with sub-RPE, subretinal, or intraretinal fluid or hemorrhage. Other clinical findings include the presence of drusen, lipid exudation, macular edema, and disciform scars in late presentations. Neovascular AMD should not be confused with OHS unless the patient presents with histo spots and PPA, as both conditions can be present.

4. Clinical management: Present and past

4.1. Vascular ablation
4.1.1. Laser photocoagulation
Beginning in the early 1970s, the use of xenon, argon, and krypton lasers proved to be beneficial for OHS patients with extrafoveal and juxtafoveal CNVs.
Cummings et al.\textsuperscript{24} demonstrated the continued long-term benefit of laser photocoagulation in OHS patients with extrafoveal and juxtafoveal CNV who were followed for a mean period of 9 years.

4.1.1.1. Extrafoveal CNVs. A multicenter, controlled clinical trial\textsuperscript{153} compared argon lasers with observation for the treatment of extrafoveal CNV in OHS patients. The trial demonstrated the superiority of argon lasers in all subgroups at every point of the 18-month follow-up. A subgroup of the MPS also analyzed the effect of argon lasers on extrafoveal OHS CNVs. The 5-year results revealed that untreated eyes had almost four times the risk of losing six or more lines of visual acuity (VA) compared with laser-treated eyes.\textsuperscript{86} Untreated eyes lost a mean of 4.4 lines of VA compared with 0.9 lines in the laser-treated group. Of particular note, 26% of the laser-treated group experienced the recurrence of the CNV in 5 years. A Canadian group compared the VA results using argon green lasers versus krypton red lasers in extrafoveal CNV secondary to OHS.\textsuperscript{154} The results demonstrated the superiority of argon laser, having a mean increase of 3 letters, compared with the krypton red group, which lost 2.5 letters.

4.1.1.2. Subfoveal CNVs. In 1993, a pilot study compared the effect of laser photocoagulation for subfoveal CNV in OHS patients. Owing to the small number of patients (n = 25), it was not possible to demonstrate the effectiveness of laser in subfoveal CNV. Both the laser-treated and the untreated groups ended with worse VA at 12 months of follow-up compared with baseline.\textsuperscript{85}

4.1.1.3. Juxtafoveal CNVs. In the context of juxtafoveal CNVs secondary to OHS, the MPS studied the visual outcomes after treatment with krypton lasers.\textsuperscript{86} The untreated group had an adjusted relative risk of 4.26 for losing six lines of VA at 5 years of follow-up. The MPS also found that better results were achieved for juxtafoveal CNV when the krypton laser covered the foveal side completely, leaving a narrow border (≤100 μm). Only 5% of these “recommended extent” lesions experienced severe visual loss (>6 lines of vision), compared with 25% of those with “less than recommended” (foveal side of the lesion left untreated) or “more than recommended” treatment.\textsuperscript{87} Therefore, failure after juxtafoveal CNV laser treatment was probably to the result of inadequate treatment (rather than lack of treatment) on the foveal side.

4.1.1.4. Peripapillary CNVs. Photocoagulation with argon or krypton lasers for peripapillary CNV or CNV nasal to the fovea proved to reduce the likelihood of losing >6 lines of vision at 3 years of follow-up, according to the MPS.\textsuperscript{86} Similar results were observed by Turcotte et al using argon or krypton lasers for CNV located in the papillomacular bundle. After treatment, 75% of eyes remained stable or improved their VA, 11% lost more than three lines of vision, 14% had changes in the optic nerve, and one eye (0.03%) developed a permanent arcuate scotoma.\textsuperscript{156}

4.1.2. Photodynamic therapy
The promising results obtained from photodynamic therapy with verteporfin (PDT) in subfoveal CNV secondary to AMD\textsuperscript{155} led to the implementation of PDT in other cases of subfoveal CNV including OHS. The Verteporfin in Ocular Histoplasmosis study was a small, uncontrolled study of 26 patients with subfoveal CNV secondary to OHS, using 50 J/cm\textsuperscript{2} at an intensity of 600 mW/cm\textsuperscript{2} for 83 seconds. At 12 months, 56% of patients gained ≥7 letters, and 16% lost ≥8 letters. These results were maintained at 24 months, with 45% of patients gaining ≥7 letters and 18% losing ≥8 letters. At 24 months, no leakage was observed in 17 of 20 classic CNV lesions.\textsuperscript{118,123} Smaller clinical studies obtained similar results.\textsuperscript{115,117,135} Busquets et al analyzed the VA outcomes of 38 patients receiving PDT for CNV secondary to OHS.\textsuperscript{18} They reported that treated patients were twice as likely to improve or maintain stable VA than those with a natural history. Sixty-nine percent of PDT-treated eyes improved or stabilized their VA, and 31% experienced a worsening of their VA at 28 weeks of follow-up. Shah et al studied the effect of PDT in juxtafoveal OHS CNVs.\textsuperscript{134} They found that 30% of eyes improved their VA by ≥3 lines, 52% remained stable, and 18% worsened. An extension report of the Verteporfin in Ocular Histoplasmosis study group evaluated the VA outcomes after 48 months of follow-up.\textsuperscript{135} Seventeen patients received at least one PDT treatment, with a mean of 4.4 treatments during the study period. Sixty percent of patients gained ≥7 letters compared with the baseline, 27% remained unchanged, and 7% lost >15 letters.

4.2. Anti-VEGF therapy
4.2.1. Role of VEGF in ocular histoplasmosis syndrome
A better understanding of molecular mechanisms revealed that the high levels of VEGF is one of the principal stimuli for the development of new, abnormal blood vessels involved in CNVs. The excellent visual outcomes achieved with anti-VEGF intravitreal injections in patients with exudative AMD supported the use of these drugs in patients with OHS CNVs. Until now, only bevacizumab and ranibizumab have been used for OHS CNVs in a few peer-reviewed case series. A clinical trial using pegaptanib for OHS is registered at clinicaltrials.gov. The study was terminated, but no results are posted. Currently, there are two clinical trials recruiting patients with active CNV secondary to OHS to evaluate the safety profile and VA outcomes using intravitreal aflibercept (HANDLE study, clinical trial #NCT01790893; and the Treatment of CNV Secondary to Presumed Ocular Histoplasmosis With EYLEA 2.0 mg, clinical trial #NCT01578720). Although the treatment of OHS CNV with intravitreal anti-VEGFs is an off-label use of the drug, its availability, efficacy, and favorable risk–benefit ratio suggest anti-VEGFs as the new standard of care.

4.2.2. Intravitreal bevacizumab
Since 2007, intravitreal bevacizumab has been used for the treatment of OHS CNVs with excellent results.\textsuperscript{1} Multiple studies have evaluated the effect of bevacizumab in CNV for disorders other than AMD, including OHS.\textsuperscript{80,93,103} A retrospective case series evaluated the VA outcomes of 28 eyes with subfoveal or juxtafoveal OHS CNV treated with intravitreal bevacizumab.\textsuperscript{136} Sixteen eyes had PDT failures, 5 received bevacizumab within two weeks of PDT (combination treatment), and 7 were PDT-naive. After a mean follow-up of
22 weeks and an average of 1.8 injections, 71% showed VA improvement, 14% stabilized, and 14% had decreased VA. Pre-treatment VA improved from 0.65 to 0.43 logMAR units. The 14% (4 eyes) that lost VA were PDT failures with progressive visual loss. PDT-naïve eyes showed a VA improvement of −0.24 logMAR units. Erlich et al used intravitreal bevacizumab in 24 treatment-naïve eyes with subfoveal or juxtafoveal OHS CNVs. At 12 months of follow-up, VA improved from 0.86 ± 0.35 to 0.34 ± 0.33 logMAR units, with 6.8 injections/year on average, and 58.3% of eyes had a final VA of 20/40 or better. A long-term study of 54 eyes evaluated the efficacy of anti-VEGFs for OHS CNVs. Forty eyes were treated with bevacizumab alone, 1 with ranibizumab and 13 with a combination of both. The mean VA roughly doubled over an average of 2 years, with 4.5 injections per patient per year.

4.2.3. Intravitreal ranibizumab

Heier et al designed a randomized study to evaluate the efficacy and safety of monthly ranibizumab injections versus three monthly doses plus PRN injections in patients with CNV secondary to causes other than AMD. Nine of the 30 patients recruited had a diagnosis of OHS. Despite the lack of stratification of the results by diagnosis, they demonstrated that 66.7% of patients in the monthly injection group gained 15 or more letters of VA at 6 and 12 months. Similarly, 64.3% and 57.1% of patients in the PRN group, gained 15 letters or more of VA at 6 and 12 months, respectively.

4.3. Surgery

4.3.1. Submacular surgery

The lack of conclusive evidence for laser photocoagulation in subfoveal CNV led to the search for other treatment options in the early 1990s. Neither PDT nor anti-VEGF injections were available at the time; therefore, a surgical approach seemed a reasonable alternative. Thomas et al were the first to describe the surgical removal of subfoveal CNV in OHS. They reported that 83% of treated eyes showed VA improvement or stabilization, with a recurrence of 37%. The same group analyzed the results of subfoveal surgery in 117 OHS patients, finding a 44% CNV recurrence. Sixty-six percent of these recurrences were located in the subfoveal region. After a median follow-up of 13 months, 35% of patients had a postoperative VA of 20/40 or better. Another report described the results of 63 subfoveal CNV eyes with OHS: VA improved in 35%, remained unchanged in 44%, and worsened in 21%. After 5 months of follow-up, 38% of the CNVs recurred. Atebara et al reported the surgical results of 17 OHS CNV eyes that were followed up for a longer period of 32 months. From the 14 eyes with subfoveal CNV, 7 achieved a postoperative VA of 20/40 or better. All three extrafoveal CNVs ended with 20/20 vision. A possible mechanism behind submacular surgery is the restoration of perfusion at the choriocapillaris. Following surgery, perfused choriocapillaris obtained a better VA outcome compared with non-perfused eyes. Interestingly, one report observed choriocapillaris atrophy after submacular surgery for OHS.

The ninth report of the submacular surgery trials (SST) investigated the benefit of submacular surgery versus observation in patients with the classic form of subfoveal CNV secondary to OHS or idiopathic causes. OHS was diagnosed in 97 of 113 patients randomized to observation and 95 of 112 randomized to surgery. The study did not report results based on diagnosis, but most patients (85% of total enrollment) had a subfoveal OHS CNV. The median VA at 24 months was 20/250 for the observation arm and 20/160 for the surgery arm, with no significant difference. Fifty-eight percent of surgically treated eyes developed CNV recurrence. They concluded that there was no benefit for submacular surgery in these patients unless VA was worse than 20/100. The 10th report of the SST group announced that vision-target quality of life improved more in patients after submacular surgery than observation. This result was refuted by the 17th SST report, which did not find any significant difference between the observation and surgery arms in median vision preference values. A prospective study with long-term follow-up (mean: 68 months) analyzed the results of 40 eyes that underwent surgical removal of CNVs due to OHS. Twenty-three eyes with subfoveal CNV had a preoperative median VA of 20/200 and mean postoperative vision of 20/50, with a CNV recurrence of 30.4%. Currently, we do not treat subfoveal OHS CNV with submacular surgery because of a high recurrence rate, as well as the availability and superiority of intravitreal anti-VEGF injections.

4.3.2. Macular translocation

Some retinal surgeons rotated the macula to a healthier RPE/choroidal bed in OHS patients with subfoveal CNV. One report included 31 eyes with previous laser photocoagulation for non-subfoveal CNV that underwent macular translocation surgery for a recurrent subfoveal CNV. The study analyzed multiple diagnoses with only 3 of 31 OHS patients. Overall, median VA improved from 20/160 to 20/80. After 6 months of follow-up, 46% gained ≥2 lines of vision, 31% remained within 2 lines of vision, and 23% lost ≥2 lines. The authors noted that 35.5% experienced intraoperative complications, and 23% developed postoperative complications (i.e., macular fold, peripheral retinal breaks, and retinal detachment). A recent report utilized 360° macular translocation in non-AMD patients with bilateral vision loss. Three of 16 patients presented with subfoveal OHS CNV. Two of these cases improved their final VA; however, one patient developed a recurrent CNV and the other, chronic cystoid macular edema. The case that did not improve also developed a recurrent CNV. All of these patients required an additional intervention such as laser photocoagulation and PDT. The use of macular translocation surgery has been abandoned because the VA outcomes are not superior to anti-VEGF injections, and the risk of perioperative complications, including proliferative vitreoretinopathy, is relatively high.

4.4. Intravitreal triamcinolone

A small retrospective study analyzed the effect of intravitreal triamcinolone for CNV secondary to OHS. Ten patients received 0.1 mg of triamcinolone for subfoveal (5/10) or juxtafoveal (5/10) CNVs. After a median follow-up of 17 months, 30% gained ≥5 ETDRS letters, 20% lost ≥5 ETDRS letters, and 50% remained stable. Four patients developed transient intraocular pressure elevation, and 4 of 9 phakic patients
developed cataracts. The authors concluded that it was a relatively safe treatment, although with such a small number of patients it is difficult to generalize this observation, especially given the above-mentioned adverse events.

4.5. Systemic therapies

Since 1961, amphotericin-B has been studied for the treatment of OHS. A small case series reported improvement in the lesions after administering intravenous amphotericin-B. Despite its initial promising results, Giles et al discouraged its use after analyzing a larger number of patients who did not show a marked improvement in their final VA. These patients also suffered from systemic side effects, especially nephrotoxicity.

Considering that inflammation likely plays a role in the pathogenesis of OHS, corticosteroids were one of the first drugs used to stabilize VA. A case series of 148 patients with subfoveal or juxtafoveal CNV secondary to OHS demonstrated that systemic or periocular steroids did not influence final VA results. After a mean follow-up of 39 months, 69.6% of patients showed poor VA outcomes of less than 20/200. Other authors have supported this observation. Another report studied 18 patients with subfoveal OHS CNV. Ten patients were treated with oral prednisone for 4 weeks and eight patients received a single triamcinolone sub-Tenon injection. After 3 months of follow-up, both groups showed stabilization of their VA, with a minor loss of 0.5 Snellen lines. A prospective interventional case series analyzed the effect of fluorocinolone acetamide implants as a compassionate use for non-AMD CNVs. Fourteen patients were assigned to high-dose sustained delivery devices, with either 2 mg (8 patients) or 6 mg (6 patients). Seven of the 14 patients had a diagnosis of OHS. After a mean follow-up of 33 months, median VA improved from 20/64 to 20/40. Ten eyes had VA improvement or stabilization. All patients developed elevated intraocular pressures and cataracts, and four eyes developed non-ischemic central retinal vein occlusion. These well-known side effects discouraged the use of corticosteroids for OHS, especially after the successful results of laser photocoagulation and anti-VEGF injections.

4.6. Combined treatment

4.6.1. Vascular ablation combined with anti-VEGF

Some authors have suggested that a combination of anti-VEGF therapy with PDT might have a synergistic effect. A retrospective case series analyzed the VA results in three treatment arms: bevacizumab injections alone, PDT failures receiving bevacizumab, and a combination arm where PDT was given within 2 weeks of a bevacizumab injection. The eyes that received combination treatment showed a greater VA improvement of −0.42 logMAR units, compared with −0.24 and 0.14 logMAR units for bevacizumab monotherapy and PDT failures receiving bevacizumab, respectively.

A large retrospective study included 150 eyes with subfoveal or juxtafoveal CNVs that received intravitreal bevacizumab (IVB) monotherapy (116 of 150 eyes) or IVB/PDT combined treatment (34 of 150 eyes). The subgroup analysis revealed that VA improved significantly from 0.82 to 0.54 logMAR units at 24 months in the subfoveal CNV group treated with IVB monotherapy. Juxtafoveal CNVs did not show a statistically significant improvement with IVB monotherapy. The 34 eyes treated with a combination of IVB/PDT did not demonstrate a statistically significant difference in either the subfoveal or juxtafoveal CNVs. In addition, VA outcomes between both therapeutic regimens did not show a statistically significant difference at any time point. A total of 93.8% of subfoveal CNV eyes in the IVB/PDT group had a 6-month treatment-free interval, compared with 76% of the IVB monotherapy group (P = 0.048). These results confirm the effectiveness of IVB monotherapy for subfoveal OHS CNV, demonstrating that the addition of PDT may increase the treatment-free intervals and decrease the number of injections.

A prospective randomized clinical trial compared VA outcomes in nine patients with OHS CNV treated with ranibizumab monotherapy or PDT. If the VA or OCT outcomes were not satisfactory by month 5, the patients would receive the alternative treatment. None of the patients in the ranibizumab group required rescue PDT, but all patients in the PDT group required rescue ranibizumab injections. The ranibizumab monotherapy group received an average of 7.7 injections (range: 1–11). The PDT group received a mean of 2.5 treatments. After 1 year of follow-up, the ranibizumab group gained 19.6 ETDRS letters, compared to 21 letters in the PDT group. No patient lost VA, and all had improved central subfield thickness on OCT.

4.6.2. Submacular surgery combined with vascular ablation

The combination of submacular surgery with vascular ablation is rarely described. As outlined previously, Shah et al studied the VA outcomes using PDT in patients with juxtafoveal CNV secondary to OHS. They reported that 16% of PDT-treated patients required submacular surgery because of the progression of their CNV. Unfortunately, no details were provided for this subgroup of patients.

5. Prevention strategies

Smoking, low levels of formal education, and increasing age are risk factors for developing CNV in OHS. A large retrospective study demonstrated that former or current smokers were nearly three times more likely to develop a CNV than controls. Low educational level was associated with a higher likelihood of developing CNV, probably because of a higher exposure to secondhand smoke. Finally, increased age showed a strong association because in this slowly progressive disease, the older the patient, the more time the CNV has had to develop. Additionally, older patients can have weaker Bruch membranes and a decreased potential for DNA repair, all facilitating CNV formation, especially in the context of cigarette smoking.

Until now, there has been no effective measure to prevent a histoplasmosis infection, nor a treatment to prevent inactive lesions from becoming CNV. A good clinical practice is to teach asymptomatic OHS patients to test themselves daily with an Amsler grid. This tool will identify symptomatic patients early in their disease course, but will not prevent the disease from occurring.
6. Conclusion

Seventy years have passed between the initial recognition of OHS as a clinical entity and the development of intravitreal anti-VEGF. OHS, a vision-threatening disease affecting young and middle-aged adults, is a clinical diagnosis made during DFE. SD-OCT has emerged as a useful tool to monitor the evolution of CNVs. It is likely that several factors are needed for the development of OHS, including a genetic predisposition, initial exposure with recurrent infections, and an immune response fighting the infection/antigen with a subsequent inflammatory reaction. Only active CNVs require treatment, which should be tailored according to their location. Laser photoagulation remains a viable option for extramacular CNVs, whereas subfoveal and juxtapfoveal CNVs are addressed with intravitreal anti-VEGF injections, PDT, or a combination of both. Corticosteroids have a marginal benefit with significant adverse effects. Although the use of anti-VEGF for OHS is an off-label indication, this is probably the current mainstream of therapy at most centers and is currently our treatment of choice for all CNV secondary to OHS. Further research in the pathogenesis and genetics of this disease is needed for the development of a potential vaccine and other specific treatment alternatives.

7. Methods and literature search

An extensive review of the literature using the keywords oculcar histoplasmosis syndrome, histoplasmosis, presumed ocular histoplasmosis, Histoplasma capsulatum, and histoplasmic choriditis was performed through Medline via the PubMed platform, Embase, and Scopus. The Related Articles function was also considered to discover additional relevant articles. Priority was given to original descriptions, multicenter, prospective, and peer-reviewed reports. Case reports were avoided unless they provided new and unique information. Review articles were not considered unless they included original descriptions. English translation was used for articles written in a language other than English.

8. Disclosure

The authors have no financial interest or conflict of interest concerning the material presented in this report.

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