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Major review

Ocular histoplasmosis syndrome

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ABSTRACT

Ocular histoplasmosis syndrome (OHS) is a chorioretinal disorder with a distinct fundus appearance that is commonly found in regions endemic for *Histoplasma capsulatum*. Choroidal neovascularization (CNV) secondary to OHS is considered one of the principal causes of central vision loss among young adults in endemic areas. Although there is no consensus regarding its pathogenesis, evidence points to *Histoplasma capsulatum* as the most probable etiology. Once considered an intractable hemorrhagic maculopathy, CNVs are now treatable. Extrafoveal CNVs are successfully treated with laser photocoagulation. Subfoveal and juxtafoveal CNVs are managed with anti-vascular endothelial growth factor therapy, photodynamic therapy, or a combination of both. Modern imaging technologies such as spectral-domain optical coherence tomography have improved our diagnostic abilities, making it easier to monitor disease activity and CNV regression. We review the epidemiology, pathogenesis, clinical manifestations, differential diagnosis, and current treatment of this disease.

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.[27] 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.

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1.1. History

Since the early 1940s, many scholars, including Reid,[116] Woods and Wahlen,[162] and Schlaegel,[128] 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[45] 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).[20,21,37–39,44,45,82,103,126,147,157] The primary infection likely occurs many years prior to the development of symptoms,[28] 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.[9,43,103,129,137]

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.[34]

1.3. Epidemiology

1.3.1. Geographic distribution

Histoplasmosis is the most endemic mycosis in the world.[33] 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.[7,22,40,64] Tennessee has the highest incidence of histoplasmosis infection in the United States.[39] Despite the worldwide distribution of the fungus, OHS has been reported in only a few countries outside the United States, including Mexico,[112] India,[136] the United Kingdom,[16] and the Netherlands.[107] 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[164] and corresponds to places with reported concentrations of histoplasmosis infections, such as excavations, old buildings, bird habitats, or caves inhabited by bats.[17,37,75,79,95] 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.[45,62]

1.3.3. Incidence and prevalence

The real incidence of OHS is largely unknown.[37] The reported prevalence of atrophic scars ranges between 1.6% to 5.3%.[7,43,137] In patients with known disease, some have estimated the incidence of neovascular lesions in the fellow eye to be up to 12% per year.[53,76,83,125,158]

Patients are at risk for marked visual disturbance, particularly after developing CNV or a subsequent macular scar.[82,105] 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.[39]

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):[45,128,162]

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.[37] 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[67] 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[138] as early as 3–4 days after the injection of live *H. capsulatum* organisms into the internal carotid artery. A subtle mottling of