



# Presumed Ocular Histoplasmosis Syndrome in the Middle East: A Case Report

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## Abstract

**Background:** Presumed ocular histoplasmosis syndrome (POHS) occurs secondary to infection with *Histoplasma Capsulatum* (HC), which is an endemic organism in many tropical areas, especially in the United States. However, it has never been proven that HC directly causes POHS, hence the name presumed ocular histoplasmosis syndrome. Patients are usually asymptomatic, but some may present with blurring of central vision.

**Case Report:** A 15-year-old girl, previously healthy, presented with a 2-months history of visual disturbance of the right eye. On physical examination, the visual acuity of the left eye was 20/20 while the right eye was only seeing “hand motion”. Fundus exam of the right eye showed juxtapapillary infiltrates with serous macular detachment, and small retinal and choroidal lesions, while the left eye showed only some small retinal and choroidal lesions. Fluorescein angiography of both eyes showed evidence of chorioretinitis with probable choroidal neovascularization (CNV). The diagnosis of POHS was made and the patient was treated with bevacizumab injections. Follow-up was done clinically and through spectral domain optical coherence tomography (SD-OCT) and showed marked improvement at the level of the macular thickness and CNV.

**Conclusion:** Diagnosing POHS can be quite challenging, especially in cases coming from non-endemic areas. Our case emphasizes the importance of considering POHS in patients presenting with visual disturbance, even in these non-endemic areas, through a careful clinical evaluation and appropriate imaging modalities.

**Keywords:** Ocular, histoplasmosis, neovascularization, histospots, bevacizumab, presumed ocular histoplasmosis syndrome.

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## Introduction

Histoplasmosis is a known endemic fungus in the United States, commonly found around the Mississippi and Ohio River Valleys [1]. According to studies, ocular histoplasmosis is present in 1.6%-12.9% of the population in endemic areas [1]. The disease seems to occur more commonly in the fourth and fifth decades, with bilateral macular involvement occurring mostly in males [1].

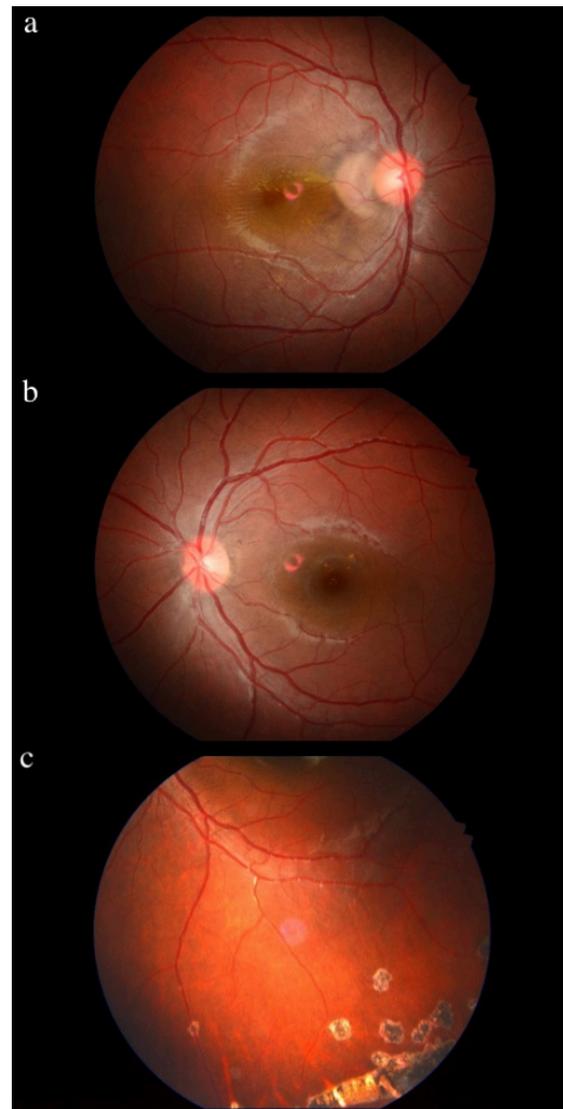
HC is transmitted to humans mainly through bat and bird droppings [2]. Common sites of dissemination include lungs, bone marrow, liver, spleen, and lymph nodes. Systemic infections are often asymptomatic, and ocular symptoms occur years after primary exposure, with ocular damage being present in only 1.6 to 5.3% of patients infected with HC [2, 3].

We hereby report a rare case of POHS in a 15-year-old girl in Lebanon, a non-endemic country for HC. This case highlights the challenge of diagnosing POHS in non-endemic areas.

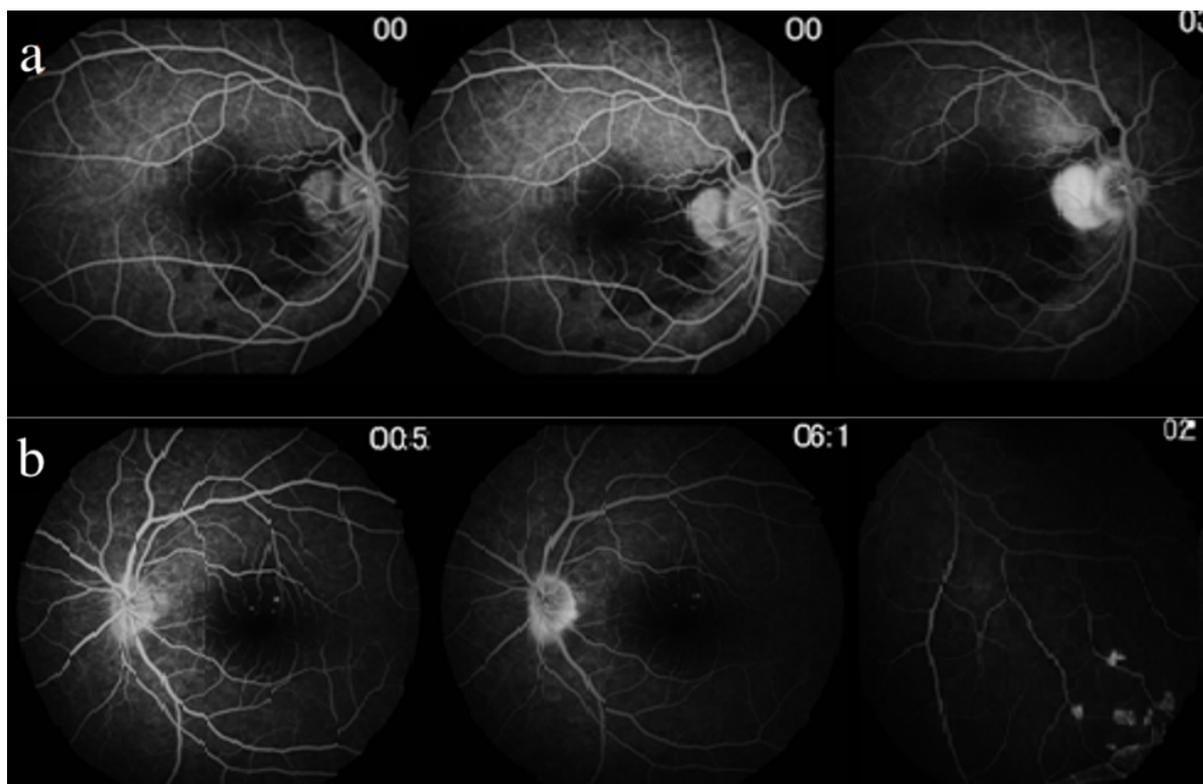
## Case Presentation

A 15-year-old girl, who is a Syrian refugee living in Lebanon, not known to have any previous medical history, presented to our clinic complaining of progressive visual disturbance in her right eye (oculus dexter, OD) of 2-months duration. On physical examination, the best corrected visual acuity (BCVA) of the right eye was only "hand motion" while that of the left eye (oculus sinister, OS) was 20/20. Slit lamp exam of both eyes showed a clear cornea. The anterior chamber was deep and clear with no signs of flare. Pupils were normal with a good pupillary reflex. The irides were normal, and the lenses were clear with no signs of cataract. Fundus exam of the right eye revealed a clear vitreous, a normal optic disc, juxtapapillary atrophy with serous macular detachment, and small atrophic chorioretinal scars or histospots (Fig 1a). In the left eye, the vitreous was clear, the optic disc was normal, but with small chorioretinal lesions (Fig 1b and 1c). Laboratory tests including complete blood

count, C-reactive protein, and erythrocyte sedimentation rate, were within normal values. Serology for *Toxoplasma gondii* was done and came back negative. Fluorescein angiography and color images showed macular hard exudates in OD and whiteish macular lesions in OS. After injection, a juxtapapillary area of early hyperfluorescence was seen in OD, increasing in size and intensity throughout the angiogram with an additional zone of dye leakage superior to the disc. Progressive optic disc hyperfluorescence



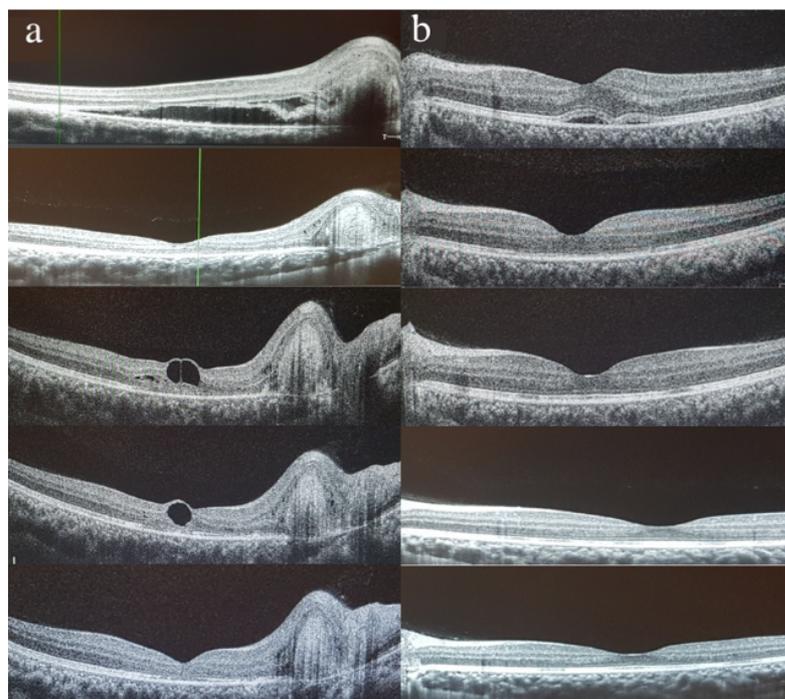
*Fig 1: Fundus photography, 1a: Fundus photography. OD showing juxtapapillary infiltrates with serous macular detachment, and small retinal and choroidal lesions. 1b: Fundus photography. OS showing peripapillary atrophy. 1c: Fundus photography of the peripheral left eye showing multiple atrophic chorioretinal scars (histospots) with some small retinal lesions.*



*Fig. 2: Fluorescein angiography. 5 days after presentation. 2a: OD, 2b: OS. Juxtapapillary area of early hyperfluorescence in OD, increasing in size and intensity throughout the angiogram with additional zone of dye leakage superior to the disc. Progressive optic disc hyperfluorescence in both eyes, and window defect hyperfluorescence at the level of the macular lesions in OS with staining of chorioretinal scars in the periphery.*

was noted in both eyes, and a window defect hyperfluorescence at the level of the macular lesions OS was noted with staining of chorioretinal scars in the periphery. This implied the presence of chorioretinitis with probable choroidal neovascularization in OD (Fig 2a and 2b), along with multiple histospots and no vitritis. Thus, the diagnosis of POHS was made. SD-OCT of the right eye showed increased central subretinal thickness (CST) of 650 microns, subretinal fluid, and evidence of a juxtapapillary neovascular membrane. However, no changes were evident on the OCT of the left eye. Two weeks after presentation, we started treatment with bevacizumab. Three intravitreal injections of bevacizumab (1.25 mg) were given to the right eye, with intervals of one month between each injection. Three months after presentation, the visual acuity of the right eye showed improvement (20/50), and SD-OCT showed a decrease in CST (310 microns) with no subretinal fluid seen (Fig 3). At four

months post-presentation, the patient showed a continued improvement of visual acuity of her right eye (20/32). However, at eight months since the first visit, the patient presented to our clinic with complaints of increased blurred vision in both eyes. Examination showed a decrease in visual acuity in both eyes (20/40 in the right eye, and 20/25 in the left eye). SD-OCT was done and showed a slight increase in CST since the last visit (330 microns), and cystoid macular edema in the right eye, as well as an increase in CST in the left eye (302 microns). Three intravitreal bevacizumab (1.25 mg) injections were applied to the right eye, with intervals of one month between each injection, and the same process was done to the left eye three weeks after the first injection was administered to the right eye. Four months later and one year after the initial presentation, SD-OCT was repeated and showed a decrease in CST in the right eye (251 microns) and left eye (211 microns) with persistent macular edema in

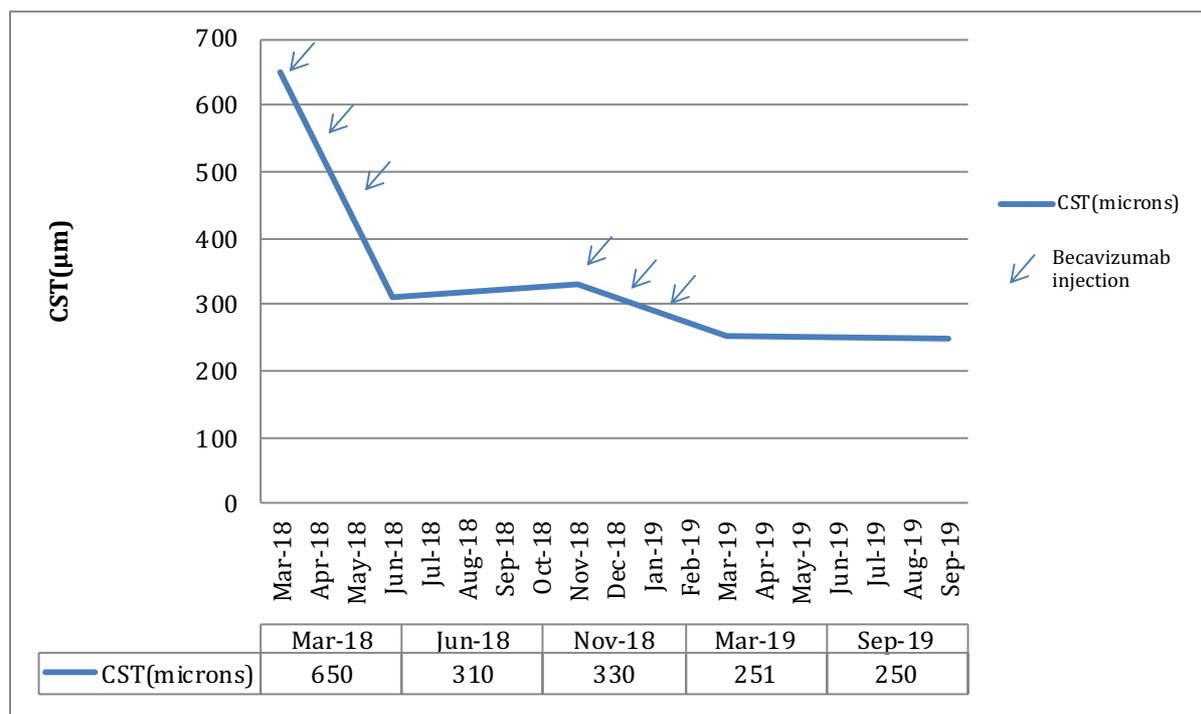


*Fig 3: SD-OCT showing evidence of increased retinal thickness, subretinal fluid, and juxtapapillary neovascular membrane. Follow-up was done after bevacizumab treatment, shown in descending order. 3a: OD, 3b: OS. Note the gradual resolving of subretinal fluid and macular edema following treatment, with the restoration of the normal foveal contour.*

the right eye. At about two years after initial presentation, SD-OCT showed a normal CST in both eyes with no macular edema present. On her final visit, almost three years after initial presentation, the visual acuity was stable at 20/25 in the right eye and 20/20 in the left eye, with SD-OCT imaging showing no signs of recurrence.

### Discussion

HC can cause two varieties of infection in the eye. The most common variety, known as presumed ocular histoplasmosis, leads to the formation of choroidoretinal scars or histospots, and possible maculopathy. The second variety is the result of disseminated histoplasmosis, in which



*Fig 4: Graph showing changes in CST of the right eye following bevacizumab treatment. Note the decrease of CST in response to bevacizumab injections.*

there is endogenous intraocular infection [4]. Posterior choroiditis caused by histoplasmosis has become a popular diagnosis since the 1959 report of Woods and Wahlen [5].

The pathophysiology of POHS remains unclear. One hypothesis states that it is caused by the inhalation of HC spores into the lung. These spores are phagocytosed by alveolar macrophages and replicate [6]. The spores then reach the blood causing fungemia, and eventually reach the eye and reside in the choroid [6]. There they cause inflammation and damage the retinal pigment epithelium and Bruch membrane, leading to the formation of chorioretinal scars. The repeated exposure to the spores causes further damage and formation of CNV [6]. Our patient did not come from and had no history of travelling to endemic areas. She also did not have a history of exposure to birds or other animals that could possibly carry the organism.

Early manifestations of histoplasmosis include circumpapillary chorioretinitis and peripheral lesions, though symptoms at this stage are uncommon. Symptoms usually ensue with the formation of CNV and can include blurred vision and metamorphopsia [7]. Lesions are not symmetrical in the initial presentation, but both eyes are commonly affected [3]. Our patient presented with progressive visual disturbance in the right eye, showing “hand motion” on acuity exam, while the left eye presented with visual disturbances a few months later. The diagnosis of POHS is based on a triad of peripapillary degenerative changes, choroidal atrophic lesions (histospots), and the presence of a clear vitreous, with or without maculopathy. The latter may present in the form of CNV [8]. On examination, our patient showed juxtapapillary infiltrates, histospots, maculopathy, and no signs of vitritis. CNV was obvious after we did a fluorescein angiography. SD-OCT is of high utility in the diagnosis and follow-up of POHS, as it provides a precise layer-by-layer analysis of the retina with a better resolution than the funduscopy or fundus

photography [9]. In our case, the use of SD-OCT, along with clinical examination were of great value to monitor improvement following bevacizumab treatment. Skin histoplasmin testing was not done due to lack of availability.

Furthermore, no direct correlation has been confirmed between ocular histoplasmosis and HC infection. A study was done on 23 patients diagnosed with POHS based on the clinical criteria mentioned above. None of these patients showed a positive antibody against histoplasmin antigen [10]. Differential diagnoses of POHS include: Sarcoidosis, tuberculosis, coccidioidomycosis, cryptococcosis, multifocal choroiditis, panuveitis, toxoplasmosis, birdshot chorioretinitis, and punctate inner choroidopathy [3]. Since HC is not clearly the cause of POHS, antifungal treatment is not usually included in the management. In one report, POHS showed no response to amphotericin B treatment [11]. The current treatment recommendations focus on CNV. These treatments have included photodynamic therapy, photocoagulation, radiation, corticosteroids, macular translocation, and submacular surgery. However, these approaches have shown a high level of recurrence and side effects. The latest treatment regimen is the intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF). Studies have shown that VEGF contributes to the formation and progression of CNV [12]. Thus, anti-VEGF seems to play an important role in the limitation of CNV secondary to POHS [13]. A retrospective study review of 54 eyes diagnosed with POHS associated with CNV and treated with anti-VEGF showed a marked improvement in the mean visual acuity from 20/53 to 20/26 over an average of 26.8 months. Only 3 patients had visual loss in a single line of vision and no major complaints were reported from any patients [14].

## Conclusion

POHS is an uncommon but potentially serious condition, that is often

asymptomatic at presentation in most cases, and typically affects patients in endemic areas. However, this condition can be seen in non-endemic areas as well, as described in our case. This makes the diagnosis even more challenging. Hence, a careful clinical evaluation is crucial to the diagnosis of such cases and to provide the appropriate treatment.

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