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Multimodal imaging of an acute presentation of ocular histoplasmosis syndrome in an immunocompetent patient

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ABSTRACT

Purpose: Presumed ocular histoplasmosis syndrome (POHS) is a posterior segment disorder that is usually subclinical unless choroidal neovascular membrane (CNVM) develops. It is thought to be the sequela of a prior systemic infection with *Histoplasma capsulatum*, and evidence supporting this association is based on epidemiologic, animal, and few enucleation studies. Acute presentation of chorioretinal involvement during an initial histoplasmosis systemic infection in immunocompetent patients is rarely reported, presumably due to the usual lack of or minimal symptoms of both the systemic and ocular disease. We report on an immunocompetent male with choroidal lesions detected during disseminated histoplasmosis infection and characterize the lesions using multimodal imaging.

Observations: A 17-year-old male presented when routine optometry screening detected two deep, yellowish-white lesions in the left fundus. Optical coherence tomography (OCT) imaging confirmed a choroidal mass with extension through Bruch's membrane into the subretinal space and a small amount of subretinal fluid. Fluorescein angiography was suggestive of CNVM. There were no clinical findings of intraocular inflammation, and the patient was initially lost to follow-up. Eight weeks after last follow-up, the patient presented to the emergency department with fatigue, mild respiratory symptoms, and abdominal pain for the last month. Imaging revealed a mediastinal mass with hilar extension and innumerable nodules throughout the lung and spleen. Serum *Histoplasma* IgM/IgG were positive, and biopsy of the mediastinal mass revealed *Histoplasma* organisms. The patient was treated with antifungals and discharged. The patient underwent an extensive immunologic evaluation while admitted, which did not reveal an underlying immunodeficiency. On last follow-up, the choroidal lesions were smaller and more consolidated, and the subretinal fluid had resolved.

Conclusions and Importance: We present a patient with choroidal lesions in the setting of disseminated systemic histoplasmosis infection and characterize a lesion using multimodal imaging. The presentation of acute chorioretinal lesions in the setting of biopsy proven systemic *Histoplasma* infection supports *H. capsulatum* as the etiology of POHS.

1. Introduction

Presumed ocular histoplasmosis syndrome (POHS) is a posterior segment disorder characterized by a classic triad of chorioretinal peripapillary atrophy, chorioretinal scars in the macula and mid-periphery (also known as "histo spots"), and the potential for development of choroidal neovascular membranes (CNVM) with associated complications such as hemorrhagic subfoveal detachment and disciform scar formation.[1] In a small minority (approximately 5%) a partial linear ring of chorioretinal scars can be found oriented parallel to the ora serrata in the equatorial region.[2] Patients are typically asymptomatic unless foveal CNVM develops and there are no other signs of intraocular inflammation; thus, the disease is often subclinical. POHS is thought to be caused or triggered by infection with *Histoplasmosis capsulatum*, one of the most widespread mycoses.[3] *H. capsulatum* infection has a high incidence in the Mississippi and Ohio river valleys within the United States (US).[1]

Gass proposed pathogenesis of the disease and its possible relation to histoplasmosis infection.[4] Briefly, an acute histoplasmosis infection

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leads to a limited disseminated disease. Patients may be asymptomatic or may have cold-like respiratory symptoms.[1] During this stage, the organism forms multiple small granulomas throughout the body, mainly in the lungs, but also involving the choroid. These granulomas are small and do not produce any ocular symptoms. Granulomas may be so tiny as to not be detected on fundus examination during this stage. In immunocompetent patients, the disease is rapidly cleared by the host immune system. In the eye, the previous nidus of infection may leave an atrophic scar. A hyperimmune reaction with recurrent lymphocytic infiltration leads to enlargement of scars and development of visible new lesions throughout time.[5] When located in the macula, CNVM may develop at the site of a lesion, resulting in visual symptoms.

Therefore, there is likely an acute granulomatous phase of the disease during initial *H. capsulatum* infection that is rarely detected. POHS is labeled "presumed" as most evidence linking the disease with histoplasmosis infection is correlational, relying primarily on epidemiologic data connecting endemic areas with the disease.[1] We report a case with follow-up of an immunocompetent patient presenting with choroidal lesions in the setting of acute confirmed disseminated histoplasmosis infection and characterize the funduscopic lesions using multimodal imaging.

2. Case report

A healthy 17-year-old male was referred by optometry for possible inflammation in the retina. The patient had been seen for an annual examination and had no ocular complaints other than mild blurring of vision in the left eye. Review of systems was negative, and past medical history was only notable for congenital sensorineural hearing loss in the left ear. He disclosed a history of living in a home with extensive mold and water damage. He is a resident of central Illinois, an endemic area for histoplasmosis.[6] Ocular examination with optometry a year prior was unremarkable per history. On initial ophthalmology exam, best corrected visual acuity was 20/20 in the right eye and 20/25-2 in the left eye. The anterior examination was unremarkable with no signs of current or past inflammation. Posterior examination was notable for two yellowish-white chorioretinal lesions in the left eye, one of which was in the inferior macula (Fig. 1A). Optical coherence tomography (OCT) of the macula demonstrated a large choroidal lesion with extending hyperreflective subretinal material, disruption of the outer retina, and surrounding subretinal fluid (Fig. 1B). The fovea had a small amount of subretinal fluid, likely accounting for the slightly decreased visual acuity. Fluorescein angiogram (FA) demonstrated early blockage with central hyperfluorescence and late leakage at the site of the macular lesion (Fig. 2). The extramacular lesion demonstrated staining in the late frames. At this visit, angiotensin converting enzyme (ACE) level, lysozyme level, syphilis antibody, and QuantiFERON-TB Gold were obtained and returned within normal limits or negative. Since the patient was asymptomatic, no treatment was recommended and the patient was referred to the uveitis service. At two-week follow-up with the uveitis service, OCT demonstrated some consolidation of the macular lesion with decreased subretinal fluid (Fig. 3). Given the lack of any clinical inflammation and improvement on OCT without treatment, close observation was recommended; however, the patient did not follow-up.

Approximately eight weeks later, the patient presented to the emergency department complaining of abdominal pain, mild chest discomfort and fatigue that had been progressive over the past four weeks. CT of the chest, abdomen, and pelvis demonstrated a heterogenous middle mediastinal mass with hilar extension, miliary pulmonary nodules, peripheral tree-in-bud opacities representing infectious or inflammatory small airway disease, and multiple ill-defined splenic lesions (Fig. 4). An extensive infectious serologic workup revealed serum anti-*Histoplasma* IgM/IgG with high levels (IgM 45.2 EU and IgG >80 EU; reference: >10.0 EU indicates a positive result). Fine needle aspiration of an enlarged lymph node demonstrated necrotizing granulomas and rare fungal yeast forms. Biopsy of the mediastinal mass demonstrated necrotizing granulomatous inflammation, and GMS stain identified yeast forms consistent with *H. capsulatum* (Fig. 5). There was a single acid-fast bacterium (AFB) detected on stain, but mycobacterium tuberculosis PCR and QuantiFERON-TB Gold were negative; infectious

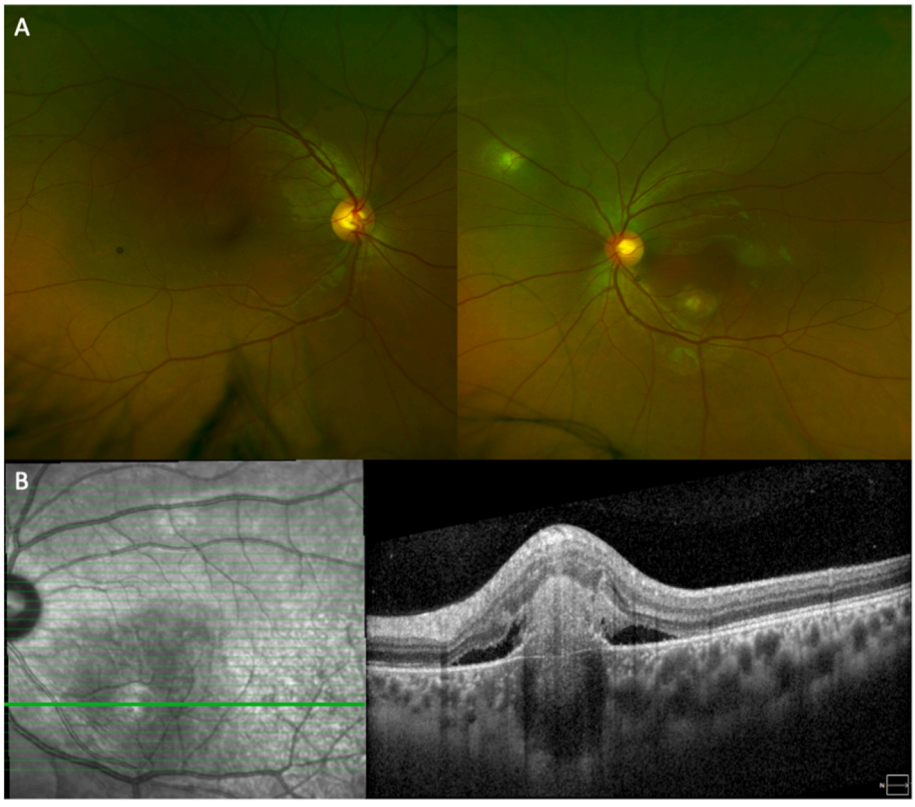

Fig. 1. Fundus photos of the right and left eye (A) and OCT of the macula of the left eye (B). Two deep, yellow-white, choroidal lesions are noted in the left fundus. OCT through the macular lesion in the left eye demonstrates a choroidal infiltrate with extension through Bruch's membrane, subretinal hyperreflective material and surrounding subretinal fluid with disruption of the outer retina. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

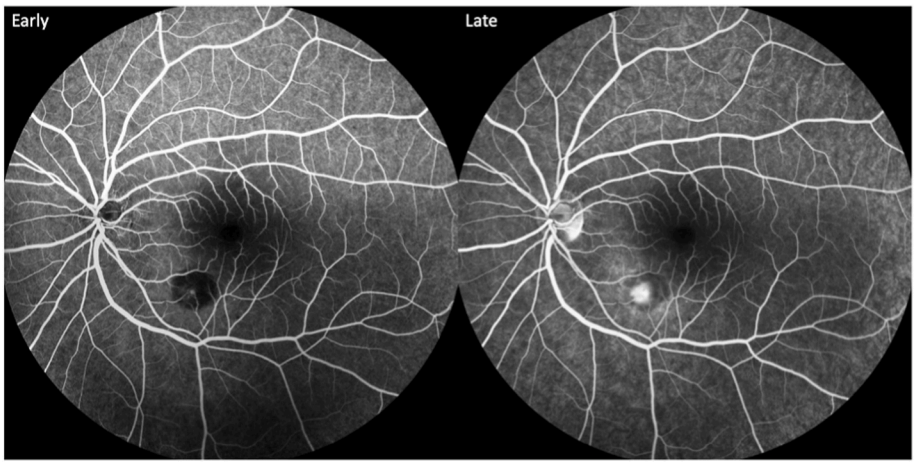

Fig. 2. Fluorescein angiography of the posterior pole of the left eye. Early frames show blockage at the site of the lesion with pinpoint hyperfluorescence. Late frames show leakage at this site consistent with a classic choroidal neovascular membrane.

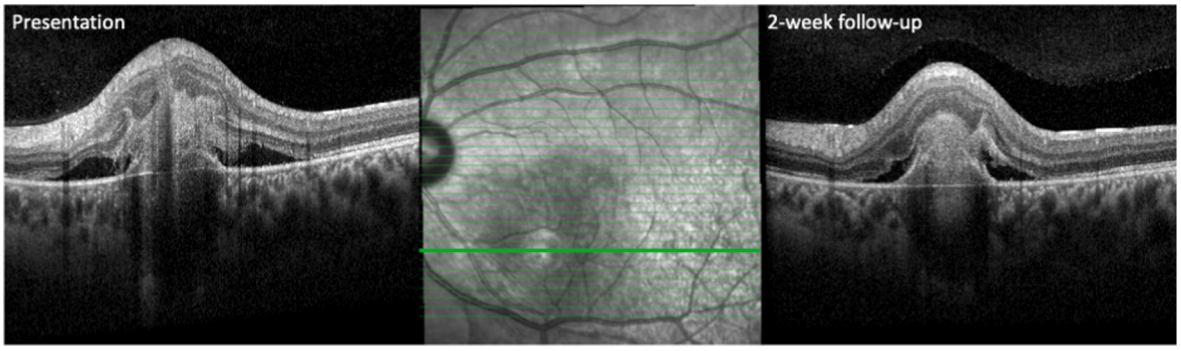

Fig. 3. Comparison of macular OCT of the left eye choroidal lesion at presentation and two-week follow-up. There has been consolidation of the subretinal hyperreflective material and interval decrease in subretinal fluid.

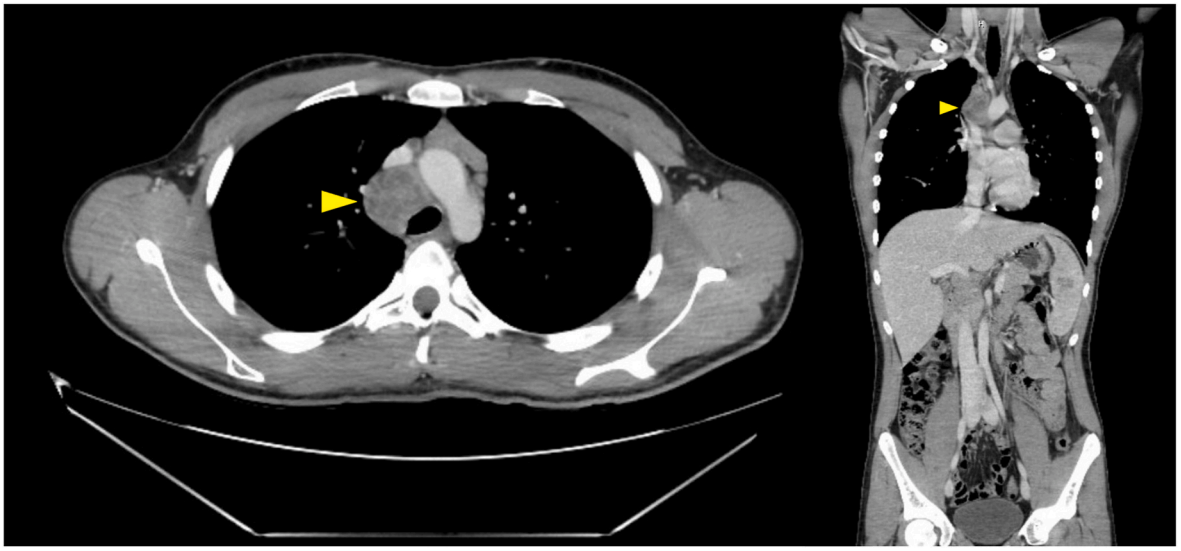

Fig. 4. Coronal and axial images from the CT of the chest, abdomen, and pelvis with contrast. Yellow arrowheads highlight the large mediastinal mass. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

disease consultants felt this was contaminant. The patient was diagnosed with disseminated histoplasmosis infection and treated with two weeks of IV amphotericin B followed by six months of oral itraconazole upon discharge, which was managed by the infectious disease service. The patient was evaluated by the immunology service given the extensive systemic granulomatous disease. Primary immunodeficiencies associated with histoplasmosis infection for which the patient underwent evaluation included STAT3 deficiency, STAT1 gain of function, GATA2

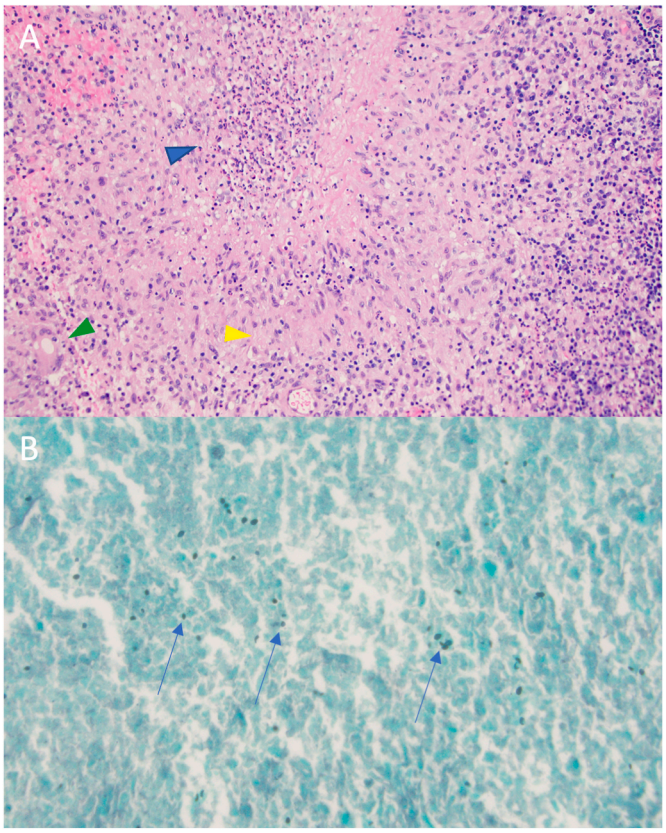

Fig. 5. Hematoxylin and eosin (H&E) stain (A) and Gomori's methenamine silver (GMS) stain (B) of the mediastinal mass biopsy. H&E stain demonstrates necrotizing granulomatous inflammation with central necrosis (blue arrowhead), multinucleated giant cell (green arrowhead) and histiocytes (yellow arrowhead). GMS stain demonstrates scattered small oval yeast forms 2–4 μm in size consistent with Histoplasma (blue arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

deficiency, chronic mucocutaneous candidiasis, hyper IgM syndrome, and defects in the IFN-gamma/IL-2 signaling pathway. Extensive immunologic evaluation for these conditions as well as immune function testing was not suggestive of a primary immunodeficiency or deficiency in immune function. Furthermore, the patient had no prior history of recurrent infections.

On last ophthalmology follow-up, approximately six months after discharge and 8.5 months after the patient's previous ophthalmology visit, the choroidal lesions were more atrophic. The patient was asymptomatic with 20/20 vision in each eye. The superonasal lesion had developed some surrounding pigmentation (Fig. 6A). The macular lesion was more consolidated with resolution of subretinal fluid (Fig. 6B). The patient was subsequently lost to ophthalmology follow-up. Of note since discharge, the patient underwent further debulking of the mediastinal mass every 4–6 months for a total of five treatments with pathology demonstrating active necrotizing granulomatous inflammation but without fungal elements.

3. Discussion

The link between *H. capsulatum* and POHS has been debated, and evidence supporting this association is mainly correlational. Epidemiologic data within the US shows a strong correlation between *H. capsulatum* endemic areas and POHS development, and several studies have demonstrated findings of past histoplasmosis infection, such as chest radiographic evidence of scarring from prior infection, in patients diagnosed with POHS.[4,7,8] Epidemiologic data have also shown

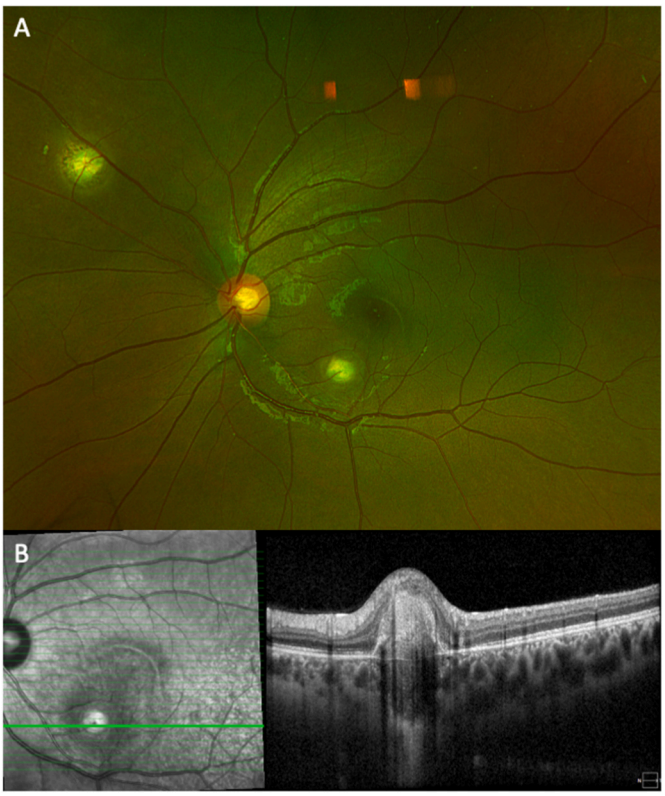

Fig. 6. Fundus photo of the left eye (A) and OCT of the macula of the left eye (B) six months after hospital discharge. The choroidal lesions appear more atrophic with pigmentation surrounding the nasal lesion. OCT through the macular lesion demonstrates a smaller choroidal infiltrate compared to baseline with continued consolidation of the subretinal hyperreflective material and resolution of the subretinal fluid.

a high rate of positivity to the histoplasmin skin test in individuals with POHS.[9,10] It is important to note, however, that there have also been studies on patients outside of endemic areas who develop a similar syndrome.[11–13]

In a previous review of 28 patients with prior positive histoplasmosis cultures, eight patients who were still alive at the time of the study were recruited for routine ocular examination. Six out of the eight were found to have asymptomatic atrophic scars consistent with POHS lesions on fundoscopic examination.[14] Furthermore, experimental monkey studies have produced choroidal lesions as well as the development of CNVM after intracarotid injection of *H. capsulatum*.[15]

Lastly, there are a few enucleation studies of patients with POHS. Ryan reported a case series of three enucleated eyes at the Armed Forces Institute of Pathology that unequivocally fit the criteria for POHS, with identification of the organism in only one patient with a large choroidal granuloma with subretinal extension. In this patient, the fundus exam some years later revealed POHS in the opposite eye.[16] Spencer et al. found products of *H. capsulatum* DNA within chorioretinal lesions of a patient with POHS who was enucleated due to an unrelated choroidal melanoma.[17] Several studies have demonstrated a choroidal lymphocytic infiltration surrounding POHS lesions.[5] Therefore, it is possible that an infectious trigger is the cause of ongoing choroidal inflammation long after the organism has been cleared from the lesions. Indeed, systemically, our patient has undergone surgical debulking of his mediastinal mass several times, which is now sterile given systemic treatment and consistently negative cultures. It is thought that this lesion represents continued reactive inflammation even though the initial infection has been cleared. A similar process may occur in the eye many years after the organism has been eradicated from the body. Our patient's immunodeficiency workup was unrevealing; it may be rather an

overactive immune response that led to the more symptomatic systemic illness and the development of the ocular findings.

Supporting the correlation between *H. capsulatum* and development of POHS is the identification of acute granulomatous disease during *Histoplasma* systemic infection. The acute disease in immunocompromised patients has been well documented, but the presentation is entirely different than that of POHS with reports of choroiditis, retinitis, and endophthalmitis, with the organism being identified at autopsy after the patient succumbed to the systemic disease.[18–21] On the other hand, acute presentations of POHS are infrequently reported given the mild to nonexistent symptoms of systemic infection and usual complete lack of symptoms in the acute phase of acute ocular disease. Indeed, to our knowledge, only one prior case with fundus photos has been published of a likely acute presentation of ocular histoplasmosis in two immunocompetent patients.[22] Katz et al. published on brothers, aged three and five years, with a mild respiratory illness of three weeks duration suspected as acute histoplasmosis based on chest X-ray findings and complement fixation assays detecting serum antibodies to *H. capsulatum* antigen. Both patients lived in endemic areas. They had incidental eye examinations seven weeks after their initial systemic illness; they were without any ocular symptoms and had 20/20 vision in each eye. Fundus photos from the report revealed a few deep, sharply demarcated, creamy-white lesions in both brothers in the macula and peripapillary area. There was no clinical inflammation on examination. Five months after initial visit, the younger brother no longer had any visible lesions, and the older brother's lesions were more atrophic with some retinal pigment epithelium (RPE) atrophy. No further follow-up was reported.

Additionally, Fowler et al. reported on an immunocompetent 16-year-old male who developed disseminated histoplasmosis with severe systemic symptoms that required hospitalization.[23] He noted bilateral floaters in both eyes. The right eye had vitreous haze, many multifocal chorioretinal lesions with a snowbank on exam, and mild vascular leakage on FA. The left eye, on the other hand, by report had two small chorioretinal lesions without any ocular inflammation, a description more classic for POHS, although fundus photography was not published. The patient did not respond to antifungals. Rather, systemic symptoms and lesions entirely resolved with systemic corticosteroids with only few areas of residual RPE atrophy. The authors postulate that the findings in this patient were due to an immune-mediated process given the rapid response to corticosteroids, supporting the notion that *H. capsulatum* is an infectious trigger for a choroidal inflammatory response. Our patient had a symptomatic and prolonged systemic illness, but in contrast to Fowler et al.'s report, eye findings were more consistent with POHS. Interestingly, there was likely a CNVM at presentation given the FA and OCT findings that regressed spontaneously, which perhaps also helped prompt detection of the syndrome.

4. Conclusions

Acute granulomatous presentations of POHS are infrequently reported given the asymptomatic nature of the systemic and ocular disease. To our knowledge, this is the first report of an immunocompetent patient who developed choroidal lesions in the context of disseminated histoplasmosis and received both multimodal imaging documentation of the fundus lesions and identification of the organism with pathologic confirmation of acute systemic infection. Our findings are consistent with Gass' proposed pathogenesis of the disease. This report further supports *H. capsulatum* as an infectious trigger for POHS.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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