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The Open Infectious Diseases Journal, 2018, *10*, 71-75

The Open Infectious Diseases Journal

Content list available at: www.benthamopen.com/TOIDJ/

DOI: 10.2174/1874279301810010071

CASE REPORT

Histoplasmosis Endophthalmitis – Case Report and Review

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Received: March 17, 2018 Revised: May 31, 2018 Accepted: June 08, 2018

Abstract:

Introduction:

Histoplasma Capsulatum (HC) is one of the most common endemic mycoses in the United States of America, and has also been reported in large numbers in various regions of Central and South America. It can cause disease ranging in severity from an upper respiratory tract-like infection, to deep single organ disease and most concerning, widely disseminated disease resulting in harmful sequelae. Presumed Ocular Histoplasmosis Syndrome (POHS) is the most common ocular manifestation of histoplasmosis and usually results in permanent disability.

Discussion and Conclusion:

In this study, we describe a rarely reported case of histoplasmosis endophthalmitis that was treated with itraconazole and resulted in almost complete resolution of all retinal findings and symptoms.

Keywords: Histoplasma capsulatum, Mycoses , Histoplasmosis endophthalmitis, Itraconazole , Caucasian, Fluorescein angiography.

1. CASE REPORT

A 27-year-old Caucasian female was evaluated for severe loss of vision in her right eye. The loss began gradually and increased in severity over a two-week period. The patient described her loss of vision as a single black speck in the center of her visual field that later increased in quantity, developed fuzzy edges, and was accompanied by floaters. There was mild retro-orbital pain bilaterally which occurred 2-3 times per week. The patient had no associated fever, chills, night sweats, shortness of breath, cough, joint pain or rash. She was evaluated by her general ophthalmologist and referred for a retinal consultation. The general examination was normal. On ophthalmologic examination, the extra-ocular movements were intact. The pupils were round, equal and reactive to light and accommodation and there was no conjunctival discoloration. Retinal-vitreal exam identified a cloudy vitreous in the right eye with significant debri. A pre-retinal white lesion was observed on the macula, suggesting fungal infection (Fig. **1**). No cupping or papilledema was observed at the optic disk. Vascular sheathing was also noted upon fluorescein angiography. The left eye was phenotypically normal.

The patient was born and lived just south of Cleveland, Ohio for the first four years of her life before moving to Illinois for one year, and then finally to the East Coast. She has traveled back and forth to Ohio several times since then, but never stayed for more than two weeks at any given time. Her most recent trip to Ohio was approximately two years before presentation for one week. During that trip, the patient denied being outside for any significant length of time, and did not report any known contact with wildlife including birds or bats. While at home in New Jersey, the patient reports sitting outside on her front porch daily just underneath a bird's nest. Past medical history was also significant for

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slight hyperopia which the patient claims has been constant since 7th grade, and precipitated her original eye exam.

Routine laboratory testing was performed. Vitreal aspirates were obtained on two occasions and were negative for bacterial and routine fungal pathogens. Because of the concern for a fungal vitritis and the patient's epidemiologic history, testing for histoplasmosis was performed in the third week of illness. Histoplasma complement fixation antibodies, and urine and serum Histoplasma antigen tests were performed. The results of this testing is presented in Table **1**.

Table 1. The results of various serologic testing from May 2016 through July 2016. Visual acuity results are also included in this table.

Test	Normal Range	May 2016 (Baseline)	May 2016 (Drug Start)	June 2016	July 2016
Histoplasma Yeast CF Antibody	<1:2	--	**1:64**	**1:32**	**1:16**
Serum HC Antigen (EU)	<5.50 EU	6.66	1.79	4.99	2.66
Urine HC Antigen (EU)	<3.50 EU	2.56	2.52	1.90>	1.12
Visual Acuity (OD)		20/350	20/200 -1	20/70	20/30 +2

Prior to definitive diagnosis, multiple therapeutic interventions were tried including treatments directed toward fungal, bacterial and inflammatory disease states, however no therapeutic response was observed. After the serologic data returned suggesting exposure to and possible active HC infection a presumptive diagnosis of HC endophthalmitis was made, and treatment with intra-vitreal steroids and concomitant itraconazole therapy 200 mg twice daily was started. Snellen visual acuity and laboratory testing was followed and improved as noted in Table **1**. Retinal vitreal examination improved as photo documented and illustrated in Fig. (**1**).

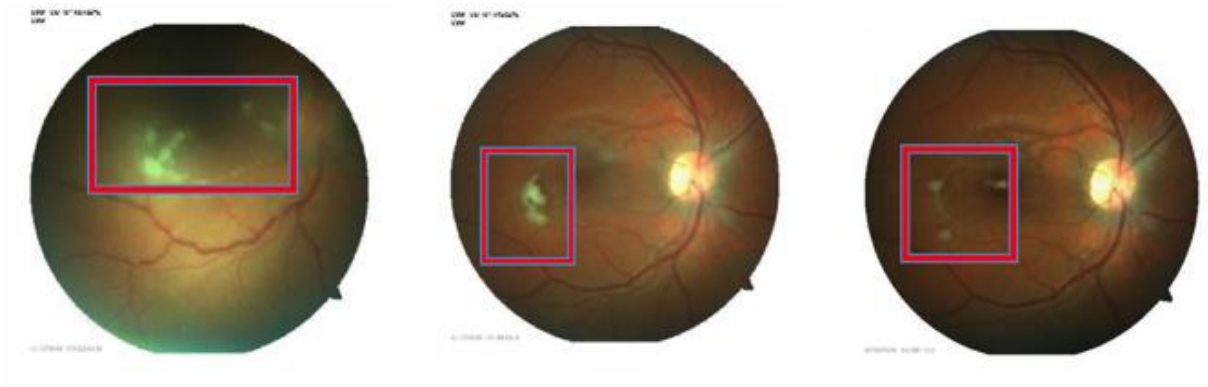

Fig. (1). The above images track the improvement of the patient on fundoscopic examination beginning in April 2016 through August 2016. A large pre-retinal abscess can be noted on the first image as well as irregular vessel structure. Improvement of the abscess and vessel structure can be observed in the subsequent pictures.

2. DISCUSSION

The most common ophthalmologic finding in HC, POHS, requires the presence of of two of the three "classic triad" signs of choroidal scars ("histo-spots"), peripapillary atrophy, and Choroidal Neovascularization (CNV), all of which can lead to severe loss of central vision. POHS treatment is normally directed toward arresting the development of further CNV through laser photocoagulation however efficacy in earlier reports seemed to be low and recurrence was common [1]. Furthermore, there is little evidence that supports treating POHS with anti-fungal medication will cure the disease or relieve the patient's symptoms [1]. Historically, many experts disagree that HC is the causative agent in patients with POHS and the evidence that links HC to POHS is largely epidemiologic [2]. A newer case report from 2012 depicts a 37-year-old immunocompetent male who presented with vision loss, and was later diagnosed with POHS. A peripheral blood sample was collected and PCR was done to detect HC. The result was later positive and sequence analysis showed a 97% similarity with the reference sequence [3]. Literature tends to support the theory that systemic histoplasmosis leading to POHS is contracted long before POHS symptoms arise in the patient [1]. It is

thought that through hematogenous spread, HC infects the eye and leaves scars that later precipitate the formation of CNV and loss of vision. The patient commonly does not have an active HC infection when they present with POHS signs and symptoms.

Our patient demonstrated evidence of an active vitreal infection with vitreal debri, vascular sheathing and a pre-retinal abscess. The retinal appearance was that of a fungal endophthalmitis. Although the cultures of the vitreous did not identify HC, the epidemiologic history, the presence of a markedly elevated complement fixation titer and positive urine and blood antigen for HC provide evidence for active HC. Furthermore, her clinical response to directed therapy is additional evidence of an active infection with HC in her eye. Although we did not identify HC from vitreal cultures, specific cultures for this were not performed. Thus we believe our patient had HC endophthalmitis.

Several other reports have been made that suggest a possible endophthalmitis due to HC [4 - 6]. Unlike our case, however, these first two reports describe scenarios in which patients were immunocompromised, and had a history significant for disseminated disease. In addition, the majority of these cases resulted in little improvement in vision or the need for enucleation of the affected eye(s) [5]. Isolated HC endophthalmitis in an immunocompetent individual was reported by Schlaen A. Et al and to our knowledge this is the only other case in which an immunocompetent host was found to have an isolated infection. However, in the case described in that report the patient had a poor response to oral itraconazole and later had to be treated with an intraocular injection of amphotericin B. Our case remains unique in that we observed a clinical response when our patient was given oral itraconazole plus intravitreal steroids [6].

Endophthalmitis is an inflammatory process of the internal structures of the eye, and can affect the uvea, retina, vitreous and sometimes the lens [7]. Our patient had significant involvement of the retina and vitreous, but did not have a past medical history of focal or disseminated histoplasmosis, was not immunocompromised, and had no involvement of the uvea or lens. We presume the patient contracted a mild, subclinical form of the disease during her childhood while she was living in Ohio. This mild illness can resemble an upper respiratory tract infection [1]. It usually does not precipitate the need to visit a clinician, however if it does, it is commonly misdiagnosed as a self-limited respiratory tract infection that resolves without medication. Later dissemination or chronic infection with HC can occur to virtually any organ [8]. Common sites of later disease include the lung, gastrointestinal (GI) tract and lymph nodes [8]. In a large retrospective report on 111 patients diagnosed with systemic HC at the Mayo Clinic, the most commonly reported extra-pulmonary symptoms included hepatosplenomegaly (49%), lymphadenopathy (39%), GI symptoms (33%), and CNS involvement (17%) [8]. Systemic disease can occur with or without immunosuppression, however in the presence of immunosuppression, dissemination can be particularly devastating involving greater hospitalization rates and treatment duration [8].

The diagnosis of HC is made by direct culture, serologic testing, pathologic examination and antigen testing. Definitive diagnosis of HC is made through isolation of the organism from direct culture from the site of infection. Direct culture entails roughly 6-12 weeks of incubation on Sabouraud agar at 25 ºC. While this method is preferred, it is not practical, because in many patients with only mild disease, culture results may still be negative. This led to the development of immunodiagnostic testing including antibody and antigen detection. Antibody testing focuses on the identification of anti-H and anti-M antibodies in the patient's serum. These antibodies are detected using histoplasmin, an antigenic extract from the fungus. It has been argued that antigen detection may be more useful in the identification of acute disease. In this case, it is postulated that antigen is released from the fungus and can therefore be detected in the serum of the patient. The tests identify the presence of a polysaccharide antigen of HC in the serum [9]. While these methods all yield different specificities and sensitivities, the results must be interpreted in the context of the patient with regard to epidemiology and risk factors in order to make a definitive diagnosis.

There are several limitations to our case. The absence of a positive culture for HC from the vitreous is of particular note. However, as discussed above the diagnosis seems likely given the results of other testing. Although the serum antigen result has a trend consistent with a therapeutic response, the value of May 2016 (drug start) could raise some concern with reliability of the testing Table **1**. However, when following the trend from May (baseline) through July of 2016 we see that the serum antigen level decreases on a month-to-month basis at a relatively steady rate consistent with a therapeutic response. We believe the May 2016 (drug start) value to be an aberrant result. Also, the limited bioavailability of itraconazole in the vitreous is of some concern in regard to the evidence of cause and effect for the outcomes we observed [9]. However, others have noted the efficacy of itraconazole therapy in the treatment of infections at other protected sites [10]. Because of concern for bioavailability the oral suspension was used to assure higher serum levels as has been demonstrated in a previous crossover study in which 30 healthy male patients were treated with both a capsule and suspension form of itraconazole [11]. Finally, the use of intravitreal steroids could be of

concern given that steroids are used in a variety of inflammatory conditions and yield strong positive results. To our knowledge only a handful of studies have been done that tried to prove the efficacy of intravitreal steroids in treating an exogenous fungal endophthalmitis. In a retrospective study that followed 20 patients with this condition, the results concluded that the use of steroids may be beneficial in promoting resolution of the inflammation associated with fungal endophthalmitis, however these results were not statistically significant [12]. With this being said, it seems that while the steroids can likely aid in the resolution of the inflammation associated with the condition, they are hardly curative, and while they may have helped our patient recover, their use cannot explain the drop in serum antigen level. Similarly, the use of intravitreal steroids has been linked to both glaucoma and cataract formation making its use somewhat controversial. A report from 2005 stated that increased ocular pressure is easily controlled with anti-glaucoma medication and those found to have cataracts can undergo surgery with no significant increase in complication rate making these side effects notable however in this case the benefits of therapy will outweigh the risks [13].

CONCLUSION

Our case represents an unusual ocular manifestation of histoplasmosis infection, endophthalmitis. Itraconazole plus corticosteroids resulted in rapid clinical response and resolution of ophthalmologic findings – which is distinctly different from what is seen in patients with POHS [14]. Although we did not obtain a positive culture from the vitreous, the epidemiologic history, laboratory testing, and response to treatment suggest this presentation is a unique manifestation of ocular histoplasmosis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are the basis of this review.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Diaz RI, Sigler EJ, Rafieetary MR, Calzada JI. Ocular histoplasmosis syndrome. Surv Ophthalmol 2015; 60(4): 279-95. [http://dx.doi.org/10.1016/j.survophthal.2015.02.005] [PMID: 25841248]

[2] Ciulla TA, Piper HC, Xiao M, Wheat LJ. Presumed ocular histoplasmosis syndrome: Update on epidemiology, pathogenesis, and photodynamic, antiangiogenic, and surgical therapies. Curr Opin Ophthalmol 2001; 12(6): 442-9. [http://dx.doi.org/10.1097/00055735-200112000-00009] [PMID: 11734684]

[3] Hernández JM, Muñoz-Cadavid CO, Hernández DL, Montoya C, González A. Detection of histoplasma capsulatum DNA in peripheral blood from a patient with ocular histoplasmosis syndrome. Med Mycol 2012; 50(2): 202-6. [http://dx.doi.org/10.3109/13693786.2011.593050] [PMID: 21732747]

[4] Goldstein BG, Buettner H. Histoplasmic endophthalmitis. A clinicopathologic correlation. Arch Ophthalmol 1983; 101(5): 774-7. [http://dx.doi.org/10.1001/archopht.1983.01040010774016] [PMID: 6601945]

[5] Gonzales CA, Scott IU, Chaudhry NA, *et al.* Endogenous endophthalmitis caused by histoplasma capsulatum var. capsulatum: A case report and literature review. Ophthalmology 2000; 107(4): 725-9. [http://dx.doi.org/10.1016/S0161-6420(99)00179-7] [PMID: 10768335]

[6] Schlaen A, Ingolotti M, Couto C, Jacob N, Pineda G, Saravia M. Endogenous histoplasma capsulatum endophthalmitis in an immunocompetent patient. Eur J Ophthalmol 2015; 25(4): e53-5. [http://dx.doi.org/10.5301/ejo.5000550] [PMID: 25612657]

[7] Chen KJ, Wu WC, Sun MH, Lai CC, Chao AN. Endogenous fungal endophthalmitis: Causative organisms, management strategies, and visual

acuity outcomes. Am J Ophthalmol 2012; 154(1): 213-4.
[http://dx.doi.org/10.1016/j.ajo.2012.03.016] [PMID: 22709846]

[8] Assi MA, Sandid MS, Baddour LM, Roberts GD, Walker RC. Systemic histoplasmosis: A 15-year retrospective institutional review of 111 patients. Medicine (Baltimore) 2007; 86(3): 162-9.
[http://dx.doi.org/10.1097/md.0b013e3180679130] [PMID: 17505255]

[9] Guimarães AJ, Nosanchuk JD, Zancopé-Oliveira RM. Diagnosis of histoplasmosis. Braz J Microbiol 2006; 37(1): 1-13.
[http://dx.doi.org/10.1590/S1517-83822006000100001] [PMID: 20445761]

[10] Felton T, Troke P, Hope W. Tissue penetration of antifungal agents. Clinical Microbiology Reviews ND; 2014; 37(1): 68-88.
[http://dx.doi.org/10.1128/CMR.00046-13]

[11] Barone JA, Moskovitz BL, Guarnieri J, *et al.* Enhanced bioavailability of itraconazole in hydroxypropyl-β-cyclodextrin solution versus capsules in healthy volunteers. Antimicrob Agents Chemother 1998; 42(7): 1862-5.
[PMID: 9661037]

[12] Majji AB, Jalali S, Das T, Gopinathan U. Role of intravitreal dexamethasone in exogenous fungal endophthalmitis. Eye (Lond) 1999; 13(Pt 5): 660-5.
[http://dx.doi.org/10.1038/eye.1999.179] [PMID: 10696322]

[13] Reichle ML. Complications of intravitreal steroid injections. Optometry 2005; 76(8): 450-60.
[http://dx.doi.org/10.1016/j.optm.2005.06.013] [PMID: 16150412]

[14] Denning DW, Tucker RM, Hanson LH, Hamilton JR, Stevens DA. Itraconazole therapy for cryptococcal meningitis and cryptococcosis. Arch Intern Med 1989; 149(10): 2301-8.
[http://dx.doi.org/10.1001/archinte.1989.00390100107024] [PMID: 2552949]