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Case Reports

Acute systemic histoplasmosis associated with chorioretinitis in an immunocompetent adolescent

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Summary

Histoplasmosis is an endemic, systemic mycosis caused by the dimorphic fungus *Histoplasma capsulatum*. A minority of patients develop asymptomatic chorioretinitis known as presumed ocular histoplasmosis syndrome (POHS), which is typically associated with chorioretinal scarring and peripapillary atrophy and occasionally with choroidal neovascularization secondary to maculopathy. We report a case of acute severe bilateral chorioretinitis associated with disseminated *H. capsulatum* in an immunocompetent adolescent boy living in an endemic area. The chorioretinitis did not respond to systemic antifungal therapy, but both his systemic illness and ocular lesions resolved with the addition of systemic steroids.

Introduction

Histoplasmosis is an endemic, systemic mycosis caused by the dimorphic fungus *Histoplasma capsulatum*. The mycelial form of the microorganism is commonly found in the dust and soil of the Mississippi River valley and Ohio River valley regions.[1] Approximately 70% of the population living in endemic areas are exposed to the fungus and react positively to a histoplasmin skin antigen challenge.[2] Primary infection is usually due to spore inhalation. The course of the disease largely depends on the number of inhaled microconidiae and the immune status of the host. In immunocompetent hosts, primary infection tends to be asymptomatic or mild and usually remits spontaneously.[1] Some patients develop presumed ocular histoplasmosis syndrome (POHS), which is associated with the following classic triad of findings: evidence of a prior chorioretinitis, development of peripheral chorioretinal scars, and peripapillary atrophy, and, in a small proportion of patients, choroidal neovascularization secondary to chorioretinal scarring.[3] In contrast, the disseminated progressive form of the disease is typically seen in patients with massive spore inhalation or immunodeficiency. Fulminant cases can present with respiratory distress, shock, disseminated intravascular coagulation, and multiple organ failure.[1] Useful diagnostic tests include serologic tests for anti-Histoplasma antibodies and Histoplasma polysaccharide antigen (HPA), silver stains of tissue sections or body fluids, and cultures from blood, bone marrow, bronchoalveolar lavage fluid, and other tissues or bodily fluids suspected to be infected based on clinical findings.[3,4] Amphotericin B and itraconazole are most frequently used to treat clinically significant infections.

We report an unusual case of acute ocular histoplasmosis and disseminated infection in an immunocompetent adolescent presenting with multiple organ involvement, including bilateral chorioretinitis refractory to systemic antifungal therapy. The acute clinical manifestations of the disease resolved with the addition of systemic steroid therapy.

Case Report

A 16-year-old African American boy presented to his pediatrician with a two-week history of general malaise,

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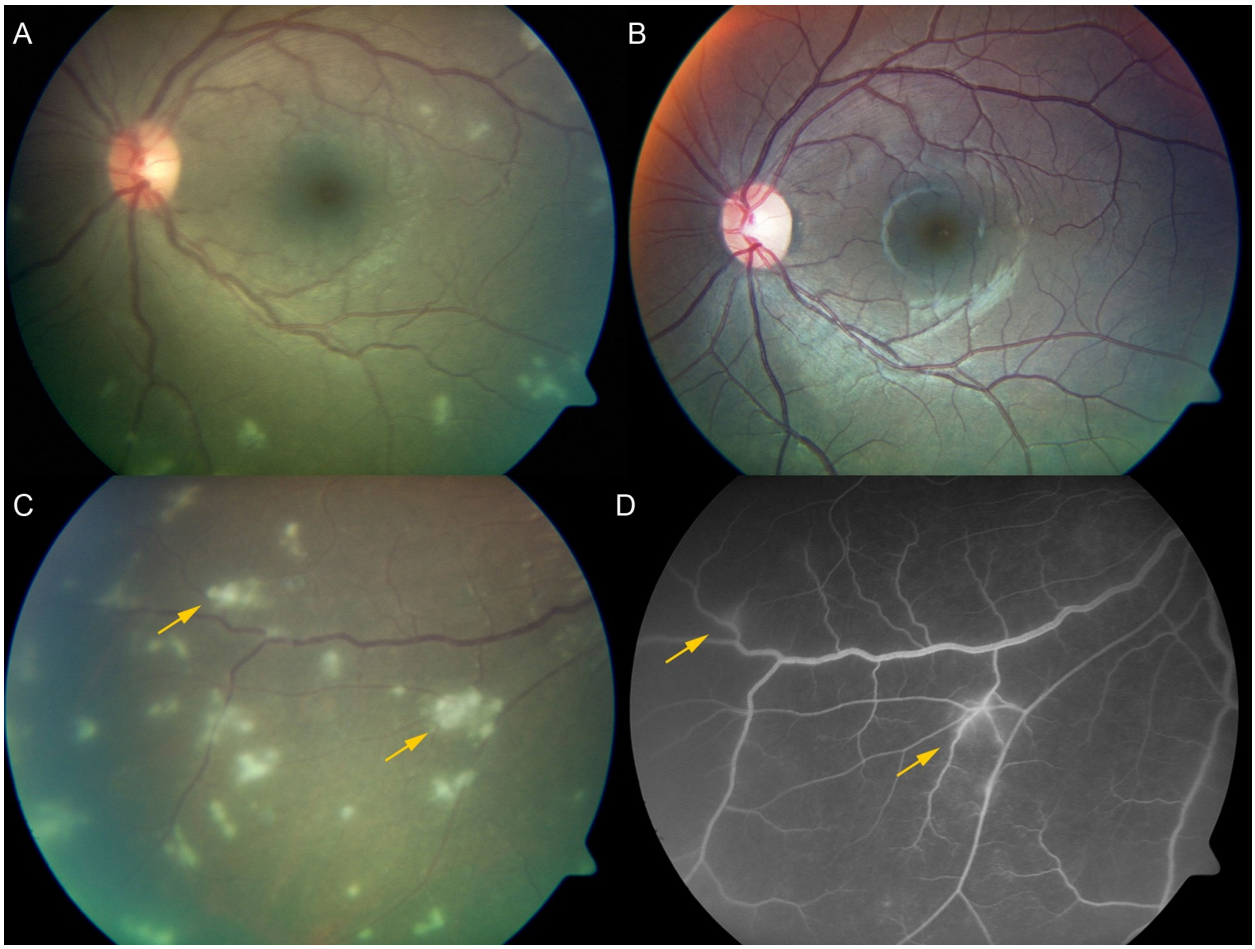

Figure 1. A, Posterior pole of the left eye at the time of presentation showing scattered inflammatory foci and mild vitreous haze. B, Resolution of the inflammation after treatment. C, Left eye at presentation showing many discrete and multifocal chorioretinal lesions in the nasal mid-periphery (yellow arrows). D, Fluorescein angiogram of the same field showing only trace dye leakage at the sites of denser lesions (yellow arrows).

pustular skin lesions, and bilateral floaters, worse in the left eye. He was treated with clindamycin for presumed bacterial infection until the onset of high-spiking fevers (T_{max} 105°F), dyspnea, and worsening malaise prompted hospitalization. The patient was on no other medications at the time of admission to LeBonheur Children's Hospital in Memphis, Tennessee. His past medical and past ocular history were unremarkable.

On initial ophthalmological examination, uncorrected visual acuity was 20/20 in the right eye and 20/20-3 in the left eye. Extraocular motility and intraocular pressure were normal, and the pupils were equally reactive. The anterior segment slit-lamp examination was unremarkable with the exception of two small fine keratic precipitates on the left cornea. On dilated fundus examination, the patient's right eye showed a normal-appearing optic nerve, posterior pole, and vasculature. There were two small areas of chorioretinitis, approximately 1/4 disc diameter in size, in the inferotemporal periphery without overlying vitritis. The left eye showed a disseminated, multifocal chorioretinitis involving the retina and choroid in the posterior pole and periphery, with snow-banking in the nasal periphery. Intravenous fluorescein angiography was remarkably benign, demonstrating an absence of leakage in the early phase and only a mild vasculitis evidenced by perivascular sheathing and focal staining in later phases, with findings of only minimal retinal inflammation at the site of the largest choroidal foci (Figure 1).

The patient was initially treated for three days with vancomycin and clindamycin for presumed bacterial infection. Blood cultures were negative, and antibiotics were

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discontinued. Since the ophthalmological examination was suggestive of fungal etiology, intravenous liposomal amphotericin B 375 mg once/day was started together with intravenous acyclovir 750 mg twice/day, pending serology results. *Histoplasma* serology titers by complement fixation were demonstrated to be markedly elevated (1:512, positive >1:8). Further, *H. capsulatum* M-band testing returned positive, indicating active or recent infection. Acyclovir was discontinued after 3 days, and amphotericin B with voriconazole was initiated. During treatment with antimicrobials, the patient's condition continued to worsen, with high fevers and increasing respiratory distress. The etiology was large bilateral pleural effusions, requiring drainage of fluid. Diagnostic testing of the pleural fluid revealed a transudate, negative for bacteria or fungi including *H. capsulatum*. Further extensive rheumatologic workup was negative. Immunologic workup revealed normal IgA, IgG, IgM, and IgE as well as a normal white blood count and differential. Infectious disease workup further revealed negative HIV serology by ELISA. Further testing was negative for toxoplasmosis, tuberculosis, sarcoidosis, and syphilis. Biopsy of the skin lesions showed pustular folliculitis, negative for bacteria or fungus, including *H. capsulatum*. Despite one week of antimicrobial therapy including systemic antifungal therapy, the patient's condition continued to worsen and intravenous steroids were started. The patient responded rapidly to steroid treatment, with resolution of fever and improvement in his respiratory symptoms beginning within twelve hours. The patient was discharged several days later on itraconazole and a six-week prednisone taper.

The patient was seen at the Hamilton Eye Institute one month following his initial presentation and was noted to have only one focal spot of residual active chorioretinitis in the peripheral retina of the left eye. Three months later the patient was asymptomatic; there was complete resolution of all active lesions, with only subtle retinal pigment epithelial (RPE) changes present (Figure 2). The resultant retinal pigment epithelium atrophy was far less than would be expected for the degree of chorioretinitis seen at initial presentation, and no "punched out" chorioretinal scars developed.

Discussion

The ocular manifestations of histoplasmosis are presumed to result from focal chorioretinal scarring after the systemic infection and inflammatory response subsides. Typical findings include punched-out atrophic chorioretinal lesions, peripapillary atrophy, and absence of vitreous inflammation. Choroidal neovascularization is the most common cause of vision loss and is estimated to occur in less than 5% of affected eyes.[5] Multifocal chorioretinitis is thought to occur in patients with sufficient immunologic capability to localize and respond to *H. capsulatum* infection. The chorioretinal lesions are generally small (<400 μm diameter) and appear oval and creamy white, with either distinct or fluffy borders.[6–8] The acute chorioretinitis is typically asymptomatic, and there are thus few case reports in the literature documenting associated findings and natural history. Several reports describe the disease in immunosuppressed children and young patients infected with the human immunodeficiency virus.[6,7] A single case report documents acute histoplasmosis choroiditis in two immunocompetent siblings.[8] Our patient presented with symptomatic active chorioretinitis prior to the development of severe systemic pulmonary and dermatologic disease. The lesions seen on the initial fundus examination were consistent with chorioretinal lesions seen in previous case reports; however, the chorioretinitis described in our patient was unusual in that it was more severe, diffuse, and also associated with significant systemic disease manifestations. Interestingly, the multifocal choroidal lesions did not scar and form the classic "punched out" choroidal lesions typically described in POHS. This mirrors the relatively benign findings seen on the initial fluorescein angiography.

POHS is considered "presumed" ocular histoplasmosis because the causal relationship between the fungus and the eye disease has not been definitively proven. In immunocompromised patients, disseminated chorioretinitis due to *H. capsulatum* during the active phase of infection has previously been described in the literature, with ocular histopathological examination confirming the presence of budding yeast characteristic of *H. capsulatum* in the choroid, retina, and central retinal vein.[3] A reproducible model of histoplasma choroiditis may be induced in primates by the injection of live *H. capsulatum* organisms via the internal carotid artery. In this model, variation in the severity of disease correlates with the size of innoculum and site of injection.[9] In a review of the clinical spectrum and treatment of classic histoplasmosis, the incidence of chorioretinitis is estimated to be between 1 to 10% in endemic areas, predominantly affecting patients between 30 and 40 years of age. Most of these patients possess the HLA-B7 or HLA-DRw2 histocompatibility complex antigen.[1,3] *H. capsulatum* has neither been observed nor cultured from the enucleated eyes of affected patients. In immunocompetent patients such as these, chorioretinitis may be an immune-mediated process. It has been proposed that the mechanism of this immune-mediated chorioretinitis is

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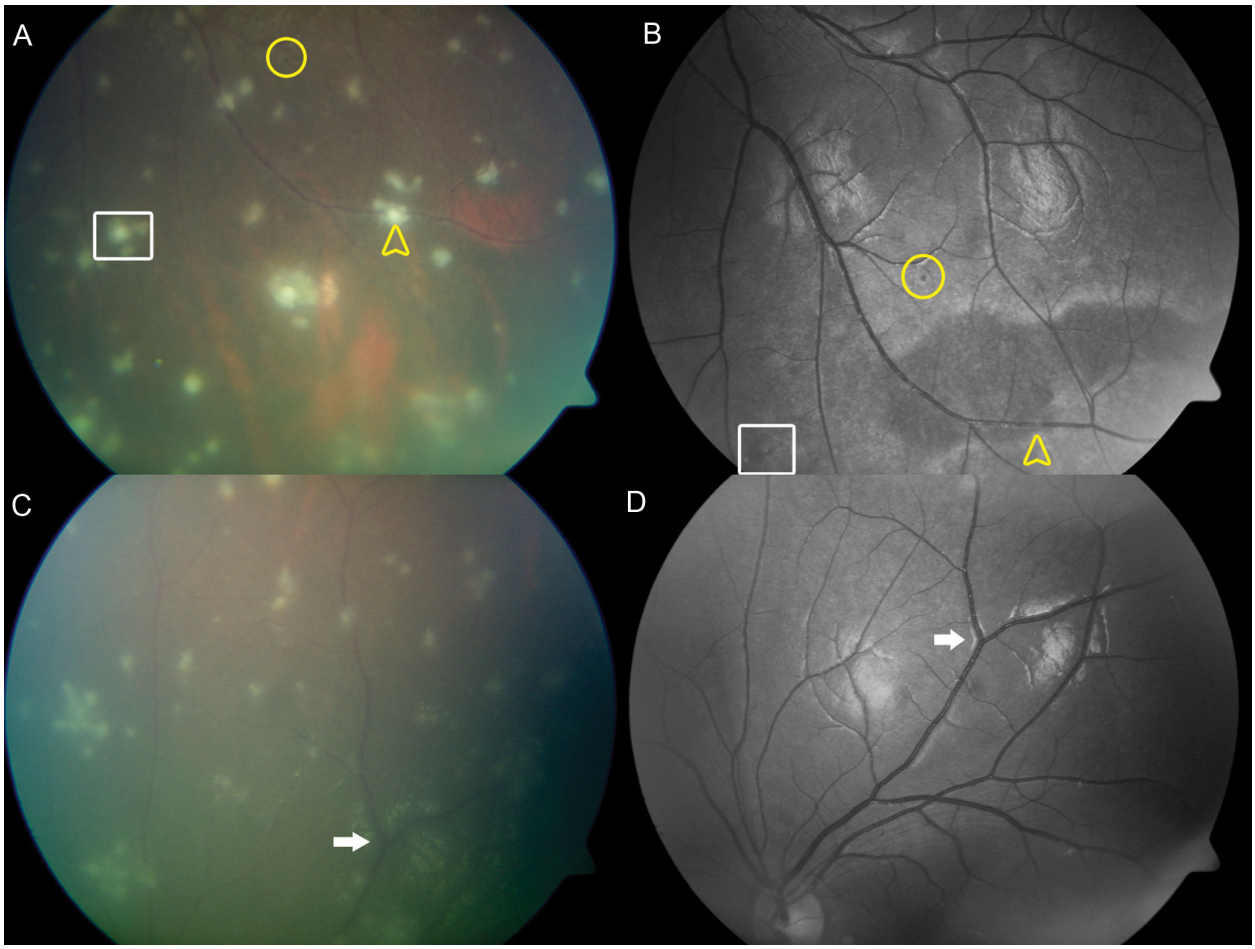

Figure 2. A, Inferior mid-periphery of the left eye at the time of presentation showing disseminated discrete and multifocal chorioretinal lesions. B, Resolution of the inflammation in the same field after treatment. A preexisting RPE scar is shown in the field (yellow circle). Only trace RPE changes (white square) and vascular sheathing (yellow arrowhead) are seen at the sites of dense lesions after resolution; most of the lesions resolved without evidence of pigmentary changes or scarring. C, Superior mid-periphery of the left eye at the time of presentation. D, Left eye after resolution of chorioretinal lesions showing no late scarring changes (white arrow marks a vessel branch point).

secondary to deposition of antigens in the choroid from pulmonary or other foci.[1,3] For the majority of cases, the chorioretinitis resolves spontaneously and antifungal and/or systemic steroid treatment might not be required. Our patient was immunocompetent but failed to respond to systemic antifungal therapy; however, he responded dramatically to steroid therapy, suggesting a primarily immune-mediated disease process.

In unusual case presentations such as this, a thorough systemic workup should be undertaken to exclude other causes of multifocal granulomatous posterior uveitis, including sympathetic uveitis, tuberculosis, toxoplasmosis, sarcoidosis, and other infectious and inflammatory processes. The patient's immunologic status is an important consideration in determining the differential diagnosis, subsequent workup, and management.

The disease presentation in this patient was remarkably asymmetric, with just a few peripheral foci in the right eye, but severe, disseminated, and multifocal disease in the left eye. Such binocular disparity may account for the asymmetry of POHS scars commonly seen in patients living in endemic areas. Despite the presence of multifocal chorioretinal lesions in the left eye, the patient did not develop the classical atrophic chorioretinal scars typically associated with POHS. We did, however, identify rare areas of pigmentary changes at the level of the RPE at the site of the most severe chorioretinal foci (Figure 2B, D).

Literature Search

PubMed (1980 to present) and Google Scholar were searched using the following keywords: *histoplasmosis*, *chorioretinitis*, and *retina*.

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