Case report

Optical coherence tomography imaging of presumed Cryptococcus neoformans infection localized to the retina

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Abstract

Purpose: To report spectral-domain optical coherence tomography (SD-OCT) findings of presumed Cryptococcus neoformans infection limited to the retina.

Methods: We report a 39-year-old male with decreased vision for 3 months. Clinical examination revealed multiple cream-colored retinal lesions in the posterior pole of both eyes. SD-OCT demonstrated multiple areas of discrete, hyperreflective deposits in the inner retina, outer retina, and subretinal space without evidence of choroidal involvement. Fundus autofluorescence demonstrated areas of hyperautofluorescence of lesions with variable areas of hypautofluorescence.

Results: Subsequent laboratory workup revealed systemic Cryptococcus neoformans infection. After 3 months of systemic antifungal treatment and follow-up, there was clinical improvement in the size of the lesions.

Conclusions: This is the first report of SD-OCT demonstrating presumed localized Cryptococcus infection confined to the retina. Our findings support the assertion that Cryptococcus can cause a focal retinitis involving all layers of the retina without demonstrable evidence of choroidal involvement.

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Keywords: Optical coherence tomography; Cryptococcus neoformans; Chorioretinitis

Introduction

Cryptococcus neoformans is an encapsulated yeast that can cause a variety of ocular manifestations in immunocompromised patients, including papilledema, cranial nerve palsies, and multifocal choroiditis.\(^1\)\(^2\) Ocular involvement occurs in up to 6% of patients with Cryptococcus meningitis.\(^3\) Unlike previous reports that have reported multifocal choroidal lesions, we describe a case of presumed ocular Cryptococcus infection where imaging findings on spectral-domain optical coherence tomography (SD-OCT) revealed presumed Cryptococcal lesions restricted to the retina.

Case report

A 39-year-old male with seizure disorder, asthma, history of treated tuberculosis, and human immunodeficiency virus (HIV), not on antiviral therapy, presented to our emergency department with malaise, fevers, cough, headache, and intermittently decreased vision for 3 months. He complained of transient vision loss that occurred when coughing or sneezing. His prior ocular history was unremarkable.

On presentation, our patient's best corrected visual acuity was 20/30 in the right eye and 20/25 in the left eye. Intraocular pressure and pupillary examination were normal in both eyes. Slit-lamp examination of the anterior segment was normal in...
both eyes. Dilated fundus examination of the right eye showed a large cream-colored retinal lesion one-disc diameter in size with intraretinal hemorrhages superior to the optic disc as well as two cream-colored retinal lesions one-quarter disc diameter in the nasal periphery (Fig. 1). Dilated fundus examination in the left eye showed a similar retinal lesion approximately one-half disc diameter superior to the optic disc, with two smaller one-quarter disc diameter lesions in the temporal periphery (Fig. 1). Fundus photography and fundus autofluorescence was obtained with the Optos 200Tx ultra-widefield imaging system. Fundus autofluorescence showed abnormal areas of hyperautofluorescence surrounding the lesions with variable hypoauflorescence centrally (Fig. 2). SD-OCT with Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) of the lesions superior to the optic disc in both eyes revealed multiple hyperreflective areas within the inner and outer retina as well as subretinal space. The choroid did not show any hyperreflectivity or localized thickening underneath the any of retinal lesions (Fig. 3). We were unable to obtain SD-OCT of the lesions in the periphery. The differential diagnosis of multiple cream or white-colored lesions in an immunocompromised HIV-positive patient is broad but should include HIV-associated microangiopathy, Cytomegalovirus (CMV) retinitis, Toxoplasmosis retinochoroiditis, syphilis retinitis, or Candida infection. A laboratory blood workup revealed negative serum reactive plasmin reagin (RPR), negative Toxoplasmosis IgG titers, and negative polymerase chain reaction test for CMV. His CD4 count was 3 with viral load of 33,507 copies/ml. He had three negative acid-fast bacillus smears from his sputum indicating no active tuberculosis as well as a negative direct fluorescent antibody test for Pneumocystis jirovecii. Subsequent lumbar puncture demonstrated elevated opening pressure of 34 cm H2O, India ink stain positive for encapsulated yeast, and Cryptococcus antigen positive titers 1:2048. Blood cultures were also positive for Cryptococcus neoformans. He was treated with intravenous amphotericin B and flucytosine for induction therapy and subsequently transitioned to oral fluconazole for maintenance therapy. Cerebrospinal cultures remained positive for Cryptococcus antigen until 3 weeks; the intracranial pressure remained elevated for 6 weeks requiring multiple lumbar punctures to lower intracranial pressure. At 3-month follow-up, there was improvement in size of lesions clinically and by SD-OCT (Fig. 3). There were also decreased areas of hyper and hypoauflorescence of the lesions in both eyes (Fig. 2). The patient was subsequently lost to follow-up.

Discussion

Cryptococcus neoformans is typically acquired through inhalation of spores and spreads hematogenously to the eye and other structures. The choroid has been definitively shown to be involved in Cryptococcus infection in multiple histopathologic studies. In a post-mortem study of 235 HIV-positive patients, Morinelli and coworkers found 7 patients with Cryptococcal choroidal involvement.4 Avendano

![Fig. 1. Color fundus photographs of the right (A) and left (B) eyes at presentation demonstrate multiple areas of creamy retinal lesions in the posterior pole with variable amounts of intraretinal hemorrhage (white arrows). Following three months of systemic antifungal therapy, lesions (white arrows) in both eyes show improvement demonstrated by less distinct borders (C and D), resolution of the hemorrhages (C) and decreased size (D).](image-url)
Fig. 2. Fundus autofluorescence photos of the right (A) and left (B) eyes at presentation demonstrate areas of hyperautofluorescence in the right eye and focal area of hypoautofluorescence with surrounding hyperautofluorescence in the left eye (white arrows), corresponding to fundus lesions. Following three months of systemic antifungal therapy, there is relative improvement of hyperautofluorescence of the lesions (white arrows) in both eyes (C and D), and resolution of area of hypoautofluorescence in the left eye (D).

Fig. 3. Spectral-domain optical coherence tomography (SD-OCT) imaging of the right eye (A) at presentation demonstrating focal hyperreflective deposit within the retina, and of the left eye (B) demonstrating focal hyperreflective deposits within the retina and in the subretinal space. There is no evidence of choroidal thickening or disruption to indicate any choroidal involvement. Following three months of systemic antifungal therapy, there is relative improvement in size of lesion but persistent hyperreflective deposits within the inner and outer retina in the right eye (C), and improved but persistent hyperreflective deposits within retina and subretinal space in the left eye (D). Again, there is no evidence of choroidal thickening or disruption.
reported the presence of fungi in the posterior choroid and choriocapillaris with preservation of Bruch’s membrane and histologically normal subretinal and retinal spaces. Andréola and coworkers reported the presence of Cryptococcus in the choroid and the subretinal space, with numerous free organisms seen in the outer and inner photoreceptor layer. Shields et al. also reported the presence of the fungi within the retina itself, although in less concentration compared to the choroid and subretinal space; they postulate that the initial lesions occur in the choroid and secondarily involve the retina. Based on their observations, Carney and coworkers suggested a 3-stage progression of ocular involvement in Cryptococcus infection; the first stage involves a chorioretinitis and optic nerve involvement, the second stage a chorioretinitis, and the third stage progressing to a uveitis/vitritis/endophthalmitis. The endophthalmitis can be severe and may not respond to systemic therapy, requiring intravitreal injections or even vitrectomy. Unlike the above reports, our patient presented with initial clinical evidence of retinitis which was only diagnosed as presumed Cryptococcal infection after cerebrospinal and serologic studies were performed. The patient’s subjective complaint of 3 months of transient vision loss with straining was likely related to his elevated intracranial pressure, which persisted even after multiple lumbar punctures. There was no clinical evidence of acute papilledema despite the elevated intracranial pressure.

To the authors’ knowledge, this is the first report of optical coherence tomography (OCT) imaging demonstrating in vivo inner and outer retinal changes in presumed Cryptococcus infection. Bailiff and coworkers initially described the findings of Cryptococcus infection on OCT. In their case report, they described focal thickening of the choroid, a continuous retinal pigment epithelium (RPE), and slight hyper-reflectivity at the photoreceptor level in the SD-OCT; however, they did not describe any inner retina changes or subretinal deposits. In contrast, our present case demonstrates primarily retinal findings on SD-OCT with large, discrete hyperreflective deposits throughout all retinal layers without any evidence of choroidal thickening. We hypothesize these retinal deposits seen on SD-OCT may represent localization of Cryptococcal organisms within the retina. These focal areas of Cryptococcus infection likely occur through the breakdown of the blood-retinal barrier through a vasculitic process. Cryptococcus has been reported to cause vasculitis in several other organs, including necrotizing vasculitis of the skin as well as small vasculopathy in the cerebral vessels leading to stroke. We were unable to obtain fluorescein angiography (FA) or indocyanine angiography (ICG) to confirm the presence of any vasculitis as our patient developed renal failure from the amphotericin B and did not give consent. FA findings have been previously described in intraocular Cryptococcus infection. Chapman-Smith et al. reported early retinal arterial leakage with subretinal staining on FA that is consistent with a vasculitic process. In contrast, Bailiff et al. reported areas of hypofluorescence without leakage on FA and localization of lesions to the choroid with ICG. In addition to our SD-OCT findings, our autofluorescence findings support our primarily retinal findings: our initial areas of hypoafluorescence due to blockage from the retinal deposits improved at 3-month follow-up, indicating the RPE and choroid were likely unaffected by the infection, otherwise we might expect persistent areas of hypoafluorescence. To the authors’ knowledge, autofluorescence findings have not been previously reported in Cryptococcus infection. We acknowledge the lack of enhanced depth imaging OCT (EDI-OCT), FA, and ICG images is a limitation in this report. Nonetheless, even without having dedicated EDI-OCT, the choroid is well visualized in our OCT images and does not show any demonstrable pathology. While microscopic involvement of the choroid cannot be ruled out with certainty without histopathological studies, the OCT images indicate that this infection was localized to the retina without any involvement of the underlying choroid.

In conclusion, our findings support the assertion that Cryptococcus can involve all layers of the retina without demonstrable evidence of choroidal involvement. Cryptococcus may cause a focal retinitis and multimodal imaging may be helpful to identify which ocular structures are involved.

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