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Case report

AIDS-related *Cryptococcus neoformans* choroiditis

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ABSTRACT

We describe a case of Cryptococcal choroiditis in a person with advanced HIV/AIDS. A 29-year-old male with AIDS presented with fever, photophobia, and ataxia secondary to cryptococcal and toxoplasma meningoencephalitis. Dilated fundoscopic examination revealed bilateral and multifocal posterior infiltrates consistent with cryptococcal choroiditis. Treatment with parenteral and intravitreal liposomal amphotericin B, oral flucytosine, and oral trimethoprim-sulfamethoxazole led to resolution of his symptoms and improvement in his vision. Our case documents a rare, intraocular opportunistic infection and highlights the importance of ophthalmologic examination in immunocompromised hosts with visual symptoms and invasive fungal infection. We discuss diagnostic and treatment considerations in cryptococcal choroiditis.

Introduction

Cryptococcal choroiditis is a rare, vision-threatening opportunistic infection (OI) in acquired immunodeficiency syndrome (AIDS) patients. Current guidelines lack advice on how best to diagnose and treat intraocular cryptococcal infection [1]. Herein, we present a case of probable cryptococcal choroiditis and a review of the literature on its diagnosis and treatment.

Case presentation

A 29-year-old male living with HIV-infection presented to our hospital with a five-day history of fever, chills, headache, photophobia, ataxia, and unintentional weight loss of 20 pounds over the past year. He reported last taking anti-retroviral therapy (ART), consisting of elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate, one year prior to admission. He reported travel to France and China five days prior to admission. His diagnosis of HIV-infection was 5 years ago and had no previous OIs. His exam revealed a fever (38.8 °C), oral thrush, intact peripheral vision, normal extraocular motility, decreased acuity, and photophobia, non-tender bilateral cervical chain lymphadenopathy, and no meningeal signs. A dilated fundoscopic examination and optical coherence tomography (OCT) were performed showing diffuse choroidal lesions bilaterally (Fig. 1A).

Admission laboratories showed a serum white blood cell (WBC) count of 2900 μL, creatinine of 0.9 mg/dL, HIV viral load of 842,000 IU/mL, and CD4 count of 8/μL. Magnetic resonance imaging (MRI) of the brain revealed multiple ring-enhancing lesions in the right frontal area, left basal ganglia, left occipital lobe and bilateral cerebellar hemispheres (Fig. 2). Lumbar puncture (LP) demonstrated an opening pressure of 23 cm H_2O and assessment of cerebrospinal fluid (CSF) showed a WBC of 4 cells/μL (56 % monocytes, 34 % lymphocytes), red blood cell (RBC) of 1 cell/μL, protein of 82 mg/dL, and glucose 22 mg/dL; CSF Gram-stain revealed many yeast and a cryptococcal antigen (CRAG) test was reactive (titer not obtained at our institution; Fig. 1B). Initial serum

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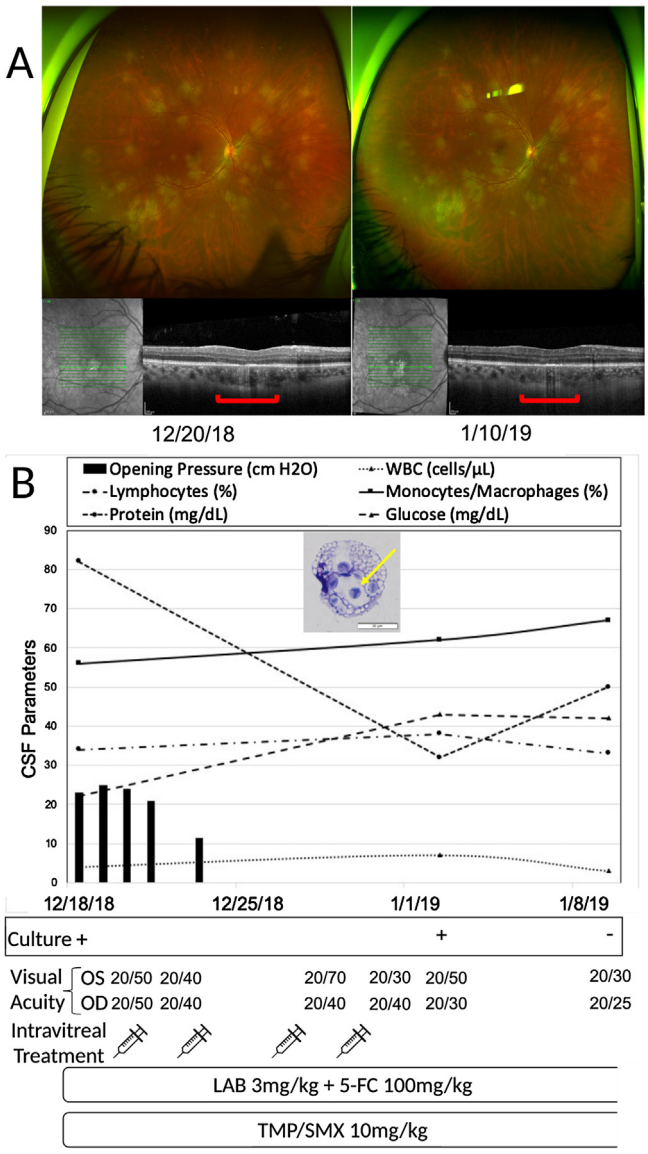

Fig. 1. Timeline of opening pressure and CSF results, CSF culture, visual acuity, intravitreal and systemic antimicrobial therapy and evolution cryptococcal choroiditis during cryptococcal induction therapy by diffuse fundoscopic examination and optical coherence tomography. A) Upper images represent diffuse fundus photography of the right eye at the start (12/20/18) and end (1/10/19) of induction/intravitreal therapy. Multifocal creamy choroidal lesions observed in the posterior pole and mid-periphery were noted to become more atrophic and pigmented following induction therapy. Lower images represent optical coherence tomography of the right eye at the start and end of therapy. Disruption of the outer retinal layers, outer retinal hyperreflectivity and underlying choroidal thickening in the macula (red brackets) were reduced at end of induction/intravitreal therapy. Diffuse fundus photography and optical coherence tomography results of the right eye are representative of those of the left eye.
B) CSF WBC, lymphocyte percentage, monocyte/macrophage percentage, glucose, protein, opening pressure and culture results, plus signs (+) indicate positive CSF culture and minus signs (−) indicate negative CSF culture. Each individual marker, bar graph, plus or minus signs represent an individual data point per day. The graph inset shows toxoplasma tachyzoites (yellow arrow) phagocytosed in macrophage from CSF. Scale bar (inset lower right hand corner) represents 20 μm. Pinhole occluder visual acuity of the right (OD; oculus dexter) and left (OS; oculus sinister) eye by Snellen chart are noted throughout time with each fraction representing an individual data point per day. The numerator represents the distance in feet between the subject and chart and denominator represents the distance at which a person with 20/20 acuity would discern the same optotype. Each syringe represents a single intravitreal treatment into both eyes of 5 μg/50 μL (per eye) liposomal amphotericin B per day. Daily dose in milligram per kilogram of liposomal amphotericin B (LAB), 5-Flucytosine (5-FC), and trimethoprim-sulfamethoxazole (TMP/SMX) are shown over time. LAB, 5-FC, and TMP/SMX treatment durations bars are open-ended on the right side to indicate extension of treatment duration beyond 1/8/19.

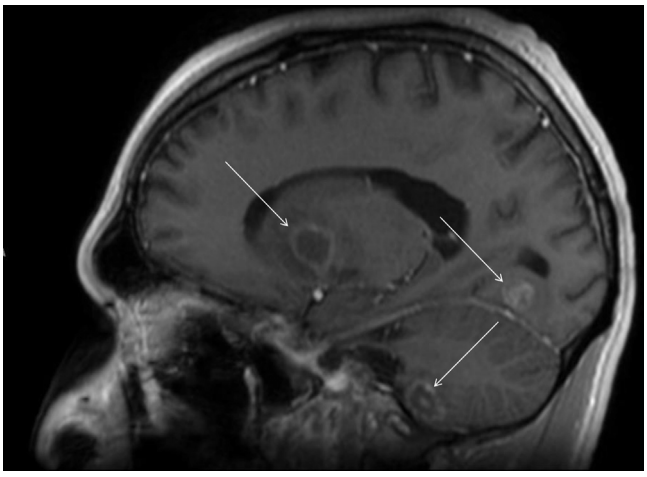

Fig. 2. MRI brain (sagittal section, multiplanar reconstruction) demonstrating multiple ring- enhancing lesions in the left basal ganglia, inferior occipital lobe, and inferior cerebellum (yellow arrows).

CRAG test was negative, however became positive following serial dilution of serum in sterile normal saline, consistent with a prozone effect [2]. CSF and blood cultures yielded *Cryptococcus neoformans* variety *grubii* (also called *C. neoformans* serotype A). Air dried cytospin preparation of the CSF stained with Diff-Quick revealed tachyzoites phagocytosed in macrophages (Fig. 1B) and toxoplasma was detected by polymerase chain reaction (PCR) in the CSF and blood (ARUP, Salt Lake City, UT).

We initiated therapy with liposomal amphotericin B, 5-flucytosine, and trimethoprim-sulfamethoxazole therapy for the treatment of cryptococcal meningoencephalitis/choroiditis and toxoplasmic encephalitis, respectively (Fig. 1B). Additionally, the patient received intravitreal injection of liposomal amphotericin B. A vitrectomy was deferred given the apparent choroidal localization on OCT (Fig. 1A). We deferred ART due to the high risk for immune reconstitution inflammatory syndrome (IRIS). Given recurrence of nausea, vomiting and headache, intermittent monitoring of the CSF opening pressure was performed, and found to be normal by the second LP. The patient had an uncomplicated treatment course notable for improvement in his vision and regression of the choroidal lesions (Fig. 1B, bottom). Upon discharge, he initiated oral fluconazole 800 mg/day following 30 days of anti-cryptococcal induction therapy with plans to restart ART after completing consolidation therapy (8 weeks of treatment). Given involution of parenchymal lesions on interval MRI brain (Fig. 2), the patient was treated with 6-week course of trimethoprim-sulfamethoxazole before transitioning to prophylactic therapy dosing.

Discussion

Cryptococcal choroiditis represents an uncommon OI of persons with advanced HIV/AIDS despite ~1 to 40 % of these patients developing neuro-ophthalmologic complications [3–8]. Intraocular cryptococcal infection was observed in 2.5%–6% of AIDS patients with cryptococcosis [9,10]. Most published cases occur from *C. neoformans* infection, though *C. gattii* is capable of eliciting a similar presentation [11]. Neuro-ophthalmologic complications that follow cryptococcosis in AIDS include diplopia, loss of visual acuity, photophobia, nystagmus, papilledema, abducens nerve palsy, optic atrophy and arachnoiditis promoting sudden visual loss [12]. The clinical course of visual loss during cryptococcal meningitis is described as rapid (< 3 days) or gradual (> 3 days), and dependent on the mechanism underlying the visual loss. Rapid

visual loss is postulated to occur by direct cryptococcal infiltration of optic nerve and arachnoiditis, while gradual visual loss is thought to result from prolonged elevated intracranial pressure and papilledema [6,13,14]. Given overlap of these syndromes, the lack of optic nerve infiltration seen on MRI and smaller rates of papilledema compared with rates of elevated intracranial pressure, Moodley and colleagues proposed optic nerve sheath compartment syndrome as a potential third mechanism implicated in cryptococcal meningitis-associated visual loss [8,15].

The prevalence of sub-clinical ocular involvement in cryptococcosis was 11 % (3 out of 27 cases) for published cases reviewed between 1968–1992 [16]. Comparatively, intraocular involvement (i.e chorioretinitis, endophthalmitis) was observed in 16 % of patients with candidemia and is frequently asymptomatic. This sub-clinical presentation underscores the Infectious Disease Society of American (IDSA) recommendation of dilated fundoscopic examination (DFE) in all patients with candidemia [17,18]. Yet, an updated endophthalmitis incidence of only ~1 % in those with candidemia calls into question the clinical utility of this screening practice [19]. Despite the possibility of similar intraocular involvement, no formal recommendation of intraocular examination screening are provided in IDSA or World Health Organization guidelines on management of cryptococcosis [20]. The presence of visual symptoms, diagnostic uncertainty of the central nervous system (CNS) lesions, and CSF/serum diagnosis of cryptococcosis in AIDS motivated a DFE in our patient.

Visual loss in the setting of AIDS entails a broad differential diagnosis. Putative etiologies include: HIV retinopathy, CMV retinitis, acute or progressive outer retinal necrosis (i.e. herpes simplex or varicella zoster virus-mediated), toxoplasma chorioretinitis, syphilitic chorioretinitis, *Pneumocystis jirovecii* choroiditis, ocular tuberculosis or *Mycobacterium avium* complex, candida, histoplasma or aspergillus endopthlamitis/vitritis, immune reconstitution uveitis, and lymphoma [21,22]. Cryptococcal intraocular infection usually manifests as infection of the posterior chamber causing choroiditis, chorioretinitis, neuroretinitis, or diffuse intraocular infection [9]. The majority of reported cases suggest hematogenous spread of yeast to the choroid layer of the posterior eye following primary infection of the lungs, though direct inoculation is also possible [16]. Extraocular infection of the CNS was observed in 81 % of those with cryptococcal ocular infection, with primary ocular disease functioning as a harbinger of later CNS involvement in 27 % of these cases [16].

The diagnosis of cryptococcal choroiditis in our patient was based on the prototypical appearance of cream-colored, bilateral, multi-focal, and intraocular/choroidal localization of the lesions, CRAG positivity in the serum and CSF, and response to parenteral and intravitreal antifungal therapy. OCT, an a optical imaging system analogous to ultrasound, enabled accurate, high-resolution microstructural localization of culprit lesions to the choroidal layer of the uvea [23,24]. Lesion localization, along with prototypical appearance on DFE, supported the likely diagnosis of cryptococcal choroiditis. In contrast, HIV-associated toxoplasma chorioretinitis presents with multifocal, bilateral lesions, described as 'headlights in a fog' on DFE as well as both choroidal and retinal involvement seen on OCT. The ring-enhancing and multifocal nature of the brain lesions we felt were more compatible with toxoplasma encephalitis than cryptococcoma, which was confirmed by detecting *T. gondii* by PCR and identification of toxoplasma tachyzoites in CSF. Real-time quantitative PCR directed against the 529bp-repeat region of toxoplasma in CSF samples of AIDS patients generated greater sensitivity and specificity for the diagnosis of toxoplasma encephalitis [25,26]. Detection of toxoplasma tachyzoites in the CSF is rare. A 12-year review of >6000 CSF cytology samples showed toxoplasma tachyzoites in only 0.03 % (2 cases) following ventricular tap only [27]. Thus, detection of toxoplasma tachyzoites from our patient's LP was exceedingly uncommon, and likely reflective of the high burden of toxoplasma in his CNS.

The standard of care for cryptococcal intraocular infection appears to be induction therapy for cryptococcal meningitis (liposomal amphotericin B and flucytosine) combined with intravitreal liposomal amphotericin B, although breakthroughs are described [28]. Treatment was initiated in our patient for cryptococcal meningitis/choroiditis and toxoplasma encephalitis, while ART was held for ~12 weeks due to the high risk for IRIS. Outcomes of cryptococcal choroiditis in the pre and early AIDS era were grim with 22 % mortality and permanent visual loss [16]. Outcomes of cryptococcal choroiditis in AIDS patients following implementation of newer oral and intravitreal treatment regimens (i.e. liposomal amphotericin B, voriconazole, isavuconazole) is currently unclear.

Penetration of liposomal amphotericin B into the eye is dependent on inflammation, and is minimal in non-inflamed eyes [29,30]. In cases of treatment failure, voriconazole (intravitreal/systemic) or isavuconazole (systemic) should be considered given the lower *C. neoformans* minimum inhibitory concentration with these agents versus liposomal amphotericin B along and their excellent penetration into the eye following systemic administration [31,32]. Our patient received ~4 weeks of systemic induction therapy because his CSF culture remained positive for *C. neoformans* after 2-weeks of induction therapy. Four weeks of induction therapy represents an intermediate duration of therapy compared to cryptococcal meningitis (1 week) and CNS cryptococcoma (6 weeks) [33,34]. Liposomal amphotericin B and voriconazole demonstrate minimal retinal toxicity following intravitreal instillation <30 μg and <250 μg, respectively. The patient was treated per current guidelines with 6 weeks of trimethoprim/sulfamethoxazole for toxoplasma encephalitis prior to transitioning to secondary prophylaxis [1].

Even in AIDS, co-infection with cryptococcus and toxoplasma is rare. Recent review of cryptococcal/toxoplasma co-infection in AIDS, shows a mortality rate of 50 % (3 out of 6 cases) [35]. Cryptococcal/toxoplasma co-infection was not observed in any stereotactic brain biopsies in a previous report of patients with AIDS [36]. In a neuropathological series of 135 autopsies in the early AIDS era, co-infection was not observed in any patient [37]. Pathological review of 35 cases of combined ocular and cerebral lesions in AIDS between 1992–1995 disclosed only 1 case of combined cryptococcal meningoencephalitis and toxoplasmic encephalitis with retinal atrophy of uncertain etiology [38].

We cannot exclude the possibility of intraocular cryptococcal/toxoplasma co-infection, despite the classic appearance of cryptococcal choroiditis on DFE and OCT. Sampling of intraocular fluid by vitreous needle aspiration or vitreous biopsy is culture positive in 69 % and 66 %, respectively, of patients with post-operative endophthalmitis [39]. However, retinal detachment was present in ~10 % of eyes. A definite diagnosis can be made by quantitative RT-PCR, membrane filtration cytology with mucicarmine staining, or CRAG assay of vitreous fluid [40–42]. Although treatment is the same for those with toxoplasmic encephalitis or ocular toxoplasmosis, a clinical response was observed in only 64 % of 199 HIV patients with extracerebral toxoplasmosis (50 % with ocular toxoplasmosis) [43]. Relapse of infection occurred in 19 % in this cohort.

Despite several attempts, telephone follow up with our patient following discharge was unsuccessful. The extent of his visual recovery, response or complication to therapy, or occurrence of relapse/persistent infection are presently unknown.

In summary, we present a rare case of cryptococcal choroiditis, meningoencephalitis, and toxoplasmic encephalitis in AIDS. Combined multidisciplinary management with infectious diseases, neurology, and ophthalmology is warranted in such cases. The presence of visual symptoms in the setting of cryptococcal

infection should prompt ophthalmology consultation and DFE. Whether all patients with cryptococcal infection warrant screening for sub-clinical intraocular infection remains unclear, though we agree with others that prospective investigation of this strategy is warranted [4]. Past outcomes appear poor in visual recovery and mortality, though are unclear given new diagnostics and emerging therapies. Though lost to long-term follow up, our patient initially improved vision and experienced successful outcome. Future studies describing outcomes of cryptococcus choroiditis following implementation of modern therapy are likely to inform a best treatment approach for this rare condition.

Declaration of Competing Interest

The authors report no declarations of interest.

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