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Cryptococcal endophthalmitis complicated by immune reconstitution inflammatory syndrome in a renal transplant recipient: A case report and review of the literature

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ABSTRACT

A 59 year old male renal transplant recipient developed endogenous cryptococcal endophthalmitis which was complicated by immune reconstitution inflammatory syndrome (IRIS). Herein we report a novel diagnostic test using lateral flow assay, the management of cryptococcal endophthalmitis and the novel complication of intraocular IRIS in a solid organ transplant recipient.

1. Introduction

Cryptococcosis is the third most common fungal infection in solid organ transplant (SOT) recipients [1]. Most infections with *Cryptococcus* spp. present as pulmonary disease with or without involvement of the central nervous system (CNS) although less common sites of infection involving other organ systems have also been reported [1]. Cryptococcal endophthalmitis is a rare manifestation of cryptococcosis and a rare cause of endophthalmitis even in SOT recipients. We report a unique case of cryptococcal endophthalmitis in a renal transplant recipient and treatment complications associated with management of his infection.

2. Case presentation

A 59-year-old male orthotopic renal transplant recipient eight years prior due to end stage renal disease caused by IgA nephropathy presented on the 2nd of September 2020 (day 0) with a ten-day history of isolated floaters in his left eye on a background of an initial kidney transplant twenty-six years prior, complicated by antibody associated nephropathy. His immunosuppressive therapy on day 0 consisted of tacrolimus 1mg mane and 0.5mg nocte, mycophenolate mofetil 500mg twice daily and prednisolone 5mg mane. Trimethoprim-sulfamethoxazole was given thrice weekly for *Pneumocystis* prophylaxis.

On examination, he had anterior uveitis and a solitary white lesion on the retina superior to the superior arcade with a small associated haemorrhage and vitritis (Fig. 1). Given the compromise to his visual acuity, he was admitted to hospital for further management. Viral and *Toxoplasma* sp. polymerase chain reaction (PCR) testing from aqueous humor were negative while a serum cryptococcal antigen was detected via lateral flow assay (LFA) returning a titre of 1:256.

Following this finding, on day 3, his ophthalmic sequelae were considered consistent with fungal endophthalmitis caused by *Cryptococcus* spp. prompting a computed tomography (CT) scan of his lungs, magnetic resonance imaging of the brain (MRI-B) and lumbar puncture (LP). The CT scan was negative for pulmonary lesions although MRI-B showed bilateral scattered periventricular and white matter hyperintensities possibly consistent with small cryptococcomas. Cerebrospinal fluid (CSF) analysis showed an opening pressure of 10.5cm of water, protein of 0.43g/L and glucose of 3.7mmol/L. India ink stain was negative for yeast cells and cryptococcal antigen was not detected in CSF.

The patient's immunosuppression was reduced and treatment with intravenous (IV) liposomal amphotericin at a dose of 3mg/kg daily and flucytosine (25mg/kg 6-hourly) initiated. This was complicated by an

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acute kidney injury and pancytopenia on day 12, nine days into therapy. Amphotericin was then replaced with oral fluconazole 400mg daily (subsequently reduced to 200mg daily due to QTc prolongation) with intravitreal amphotericin B 5microg twice weekly.

On day 23, a repeat vitreous sample was pursued to confirm cryptococcal endophthalmitis given treatment complications. Microscopy was negative for fungal elements and yeast cells, and no fungus was cultured after four weeks of incubation. Because microscopy was negative and there was only a low grade vitritis at the time, PCR testing was not performed at this time, although this was subsequently performed and negative on day 36. Following microscopy, 50 μL of vitreous humor was diluted to two-hundred-fifty microliters due to limited specimen volume and tested for cryptococcal antigen via LFA returning a titre of 1:80. LFA is not validated for testing in vitreous humor however within these limitations, we believe that this is the first such case diagnosed via LFA in humans.

On day 27, oral prednisolone was increased to 50mg daily, as adjunctive treatment of inflammatory chorioretinitis and slowly weaned over 4 months. On day 160, when a prednisolone dose of 12.5mg was reached, there was a marked deterioration in visual acuity with a resurgence of perilesional chorioretinal inflammation and vitritis consistent with immune reconstitution inflammatory syndrome (IRIS). This resolved after increasing prednisolone to 25mg daily followed by a slow taper. The patient was managed with weekly intravitreal amphotericin B injections for 12 months total at which point his infection and inflammation was quiescent. He continues to be seen at 18 months since his initial presentation without further relapse. His current treatment regime includes oral fluconazole alone to be continued as long term therapy.

3. Discussion

While an uncommon pathogen in immunocompetent individuals, the potential for *Cryptococcus* spp. to cause disseminated fungal infection in the immunosuppressed is well known [2]. The overall incidence of infection with *Cryptococcus* in SOT recipients is estimated around 2.8% but can range between 0.2 and 5% [1]. Once infected, there is a particular tropism to the CNS via haematogenous spread, although any organ system may be involved. Up to one third of SOT recipients with *Cryptococcus* infection have an associated fungemia and 48–89% of SOT patients develop CNS involvement [1,3].

Endophthalmitis from cryptococcal infection is rare, via haematogenous inoculation to the choroidal vascular bed [4]. To date, there are only two cases of ocular cryptococcosis in SOT reported in the literature in addition to the presented case (Table 1) [5,6]. Although cases of isolated ocular involvement have been reported in the literature, cryptococcal chorioretinitis in conjunction with meningitis or meningoencephalitis is more common. In our reported case, there was initial suspicion that scattered periventricular hyperintensities seen on MRI could represent cryptococcomas although CSF analysis, fungal cultures and antigen testing of CSF fluid was unsupportive.

Cryptococcal endophthalmitis is generally diagnosed based on antigen testing or culture from extraocular areas supported by an abnormal eye exam [7]. Where sampling is required, microscopy and culture are the main diagnostic modalities [7]. In the presented case, due to treatment complications, we attempted to re-confirm the diagnosis after initial vitreal humor cultures returned negative. The presence of cryptococcal antigen in repeat vitreal sampling helped confirm the diagnosis, in what we understand to be the first instance of cryptococcal antigen testing performed on human vitreous humor.

Previous investigators looking at the utility of cryptococcal antigen in vitreal fluid in rabbits showed a 100% sensitivity [9]. Its performance in human samples is uncertain and not validated however, particularly when dilution is required to obtain minimum specimen volumes required to conduct the assay. In our case, a titre of 1:80 given the five-fold dilution would represent a titre of 1:320 if conducted neat. Based on our experience, we would suggest that LFA could be considered in cases where microscopy and culture are negative and clinical suspicion remains high.

In the absence of high quality randomised controlled trials devoted to cryptococcal endophthalmitis in SOT recipients, treatment guidelines are extrapolated from experience in those with cryptococcal endophthalmitis secondary to human immunodeficiency virus [8,9]. Backbone therapy includes systemic antifungal therapy complemented by direct intravitreal antifungal injections, and consideration of systemic and local corticosteroids to reduce the inflammatory burden on the retina, with close monitoring for potential treatment complications especially in the acute phase.

Fungal antibiograms are often delayed or unavailable to guide the choice of intravitreal agent and the absence of antifungal breakpoints means it is difficult to draw definite conclusions regarding optimal therapies. In the initial setting, amphotericin B is the most common first-line empiric agent used. More recently, other antifungals including voriconazole and fluconazole have been shown to be equally effective especially when used in combination therapy [10].

Adjunctive intravitreal injections of antifungal agents with systemic antifungals are recommended to bolster ocular antifungal concentrations given the poor penetration of systemic therapy especially in the immediate phase of treatment [2]. Intravitreal therapy should be given at the first available opportunity, with a reassessment and consideration of further injection at 48 hours and then at decreasing intervals. This should continue until the lesion, surrounding retinitis and vitritis resolve on clinical examination. Amphotericin B is the most common first line agent used at a dose of 0.05–0.10 μg in 0.1ml although retinal toxicity and necrosis has been reported in animal models at these doses [11]. For this reason intravitreal voriconazole at 100 μg in 0.1ml may be preferred [11].

In addition to the direct toxic effects of systemic antifungal therapies, IRIS is a well-known complication associated with the treatment of cryptococcosis occurring as a pro-inflammatory process due to T cell dysregulation [12]. An estimated 5–11% of SOT recipients with cryptococcal disease develop IRIS typically occurring four to six weeks

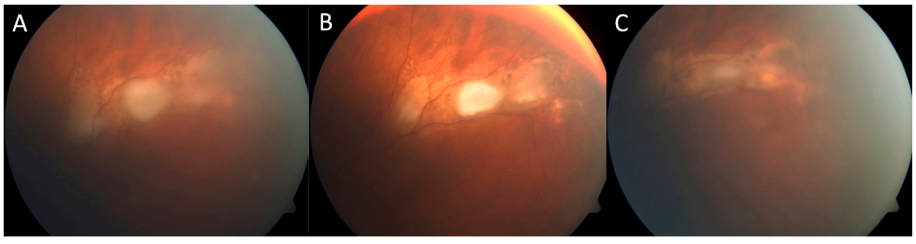

Fig. 1. Colour fundus photographs showing evolution of the cryptococcal endophthalmitis over time. A. Choroidal cryptococcoma with vitritis and retinitis at the time of diagnosis. B. Occurrence of ocular IRIS at three months post diagnosis with a rounded "fluffy" choroidal lesion. C. Scarred choroid and retina and quiescent lesion at 11months post diagnosis. Note the concave lesional borders from scar formation. Poor view due to significant posterior subcapsular cataract. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
All reported cases of cryptococcal endophthalmitis in solid organ transplant recipients in the literature.

Author	Year	Age	Gender	Affected side	Transplant Type	Baseline Immunosuppression	VA on presentation	Diagnostic Method	Systemic Treatment and duration	Intravitreal Treatment and duration	Outcome
Agarwal	1991	37	M	Bilateral	Renal	Azathioprine 125mg/day and prednisolone 15mg/day	Right 6/6 and Left 6/36	Positive India ink stain on CSF	6weeks of amphotericin B - total dose 1.75g. Changed to fluconazole 200mg/day for 8 weeks, then 100mg/day as ongoing maintenance therapy	Nil	6/5 and 6/24
Biswas	1998	37	M	Left	Renal	Azathioprine 100mg PO followed by Cyclosporine 200mg; Prednisolone 10mg PO	Blurred	CSF from LP	IV Fluconazole 200mg/day for 10 weeks. Then 200mg/day PO for 4 weeks.	IVT amphotericin B after 6months fluconazole added.	Right Eye 6/6 and Left eye eviscerated
Present Report	2022	59	M	Left	Renal	Tacrolimus 1mg mane and 0.5mg nocte; Mycophenolate mofetil 500mg BD; Prednisolone 5mg mane	6/7.5	Crytococcal antigen lateral flow assay on diluted vitreous. Titre 1:80	IV liposomal amphotericin 3mg/kg/day and Flucytosine 25mg/kg QID for 9 days. Then oral fluconazole 400mg/day.	Amphotericin B twice weekly for 6 weeks and then weekly for 7months until quiescent	6/60 + 1

following treatment initiation [12]. While net immunosuppression should be reduced as an adjunct to antifungal therapy, each case needs to be individualized and changes made cautiously as rapid reduction in immunosuppressive therapy may lead to graft rejection and IRIS [1].

Management of this reported case was complicated by intraocular IRIS. Although intraocular IRIS has been well studied in HIV patients on anti-retroviral therapy, optimal treatment in SOT patients is less well understood. The diagnosis of IRIS was made when an acute vitritis flare followed the rapid weaning of oral steroids. Re-initiation of steroid therapy at higher doses resolved the patient's symptoms and confirmed the diagnosis of IRIS.

The management of IRIS should be individualized, but generally requiring a slow wean of steroids that is titrated against the patient's ocular signs. We believe this to be the first case of intraocular IRIS in a non-HIV solid organ transplant recipient reported in the literature.

In conclusion, cryptococcal endophthalmitis is a progressive, vision threatening disease particularly in immunosuppressed patients. We report a novel approach to diagnosis of endogenous cryptococcal endophthalmitis using vitreal cryptococcal antigen detection and our experience managing the risk-benefit profile of treatment using targeted intravitreal therapy. We propose further investigation into the performance of vitreal cryptococcal titre analysis as a way of facilitating rapid diagnosis of this serious intraocular infection, as well as additional research to elucidate the optimal duration and route of therapy for both cryptococcal chorioretinitis and ocular IRIS.

Declaration of competing interest

There are none.

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