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Case report

Cryptococcal endophthalmitis and meningitis in an immunocompetent middle-aged woman: A case report

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ABSTRACT

Cryptococcus neoformans is a global invasive mycosis that is known to cause significant morbidity and mortality. It is commonly observed that individuals with compromised immune systems are more prone to developing cryptococcal meningitis. Although ocular involvement is rare, previous studies have indicated that ocular lesions precede symptomatic meningitis in only 27 % of patients with central nervous system involvement. Intraocular infections typically manifest as chorioretinopathy and vitreous inflammation, often leading to severe vision loss. In this case, we present the clinical details of a 57-year-old immunocompetent woman who visited the ophthalmology department of West China Hospital of Sichuan University with a progressive loss of vision in her right eye. After a thorough evaluation, she was diagnosed with fungal endophthalmitis, and subsequently initiated on appropriate induction anti-fungal therapy for cryptococcal meningoencephalitis. This case highlights the importance of early recognition and treatment, which can potentially improve the prognosis for patients.

Introduction

Cryptococcus neoformans is a budding yeast with a prominent polysaccharide capsule. It is widely distributed in the environment, particularly in areas with bird excreta, and has a global presence. This pathogenic organism affects three main groups of individuals: (1) those infected with human immunodeficiency virus (HIV), (2) organ transplant recipients, and (3) non-HIV-infected and nontransplant hosts [1]. Systemic cryptococcosis most commonly involves the lung, brain, and meninges [2]. While ocular cryptococcosis is rare in nonimmunosuppressed patients, it can manifest as optic papilloedema, optic nerve atrophy, extraocular muscle paralysis, chorioretinitis, and endophthalmitis [3]. In this case report, we present the clinical course of a middle-aged immunocompetent woman who developed acute chorioretinitis and endophthalmitis following cryptococcal infection. Subsequently, she developed neurological symptoms and was diagnosed with cryptococcal meningitis by detecting Cryptococcus neoformans in her cerebrospinal fluid. The patient was treated with a combination of amphotericin B deoxycholate (AmBd) and 5-fluorocytosine (5-FC), leading to gradual recovery.

Case presentation

A middle-aged woman with a history of gradually declining vision in her right eye for 11 months presented at the emergency department of West China Hospital of Sichuan University. She denied experiencing any nausea, vomiting, neck stiffness, headache, delirium, or confusion. The patient was diagnosed with "acute retinal necrosis of the right eye" and referred for ophthalmology treatment. Her visual acuity was measured at 20/40 in the right eye and 20/20 in the left eye. Intraocular pressure was recorded as 9.6 mmHg and 13.3 mmHg in the right and left eyes, respectively. The examination of the right eye revealed 1 + keratic precipitate, 2 + anterior chamber flare, a 6 mm pupil diameter with delayed light reflex, posterior synechia of the iris at the 3–4 o′clock position, pigmentation visible on the anterior surface of the lens, vitreous opacity, and 6 PD size gray-white lesions in the supratemporal region of the retina (Fig. 1A). Laboratory studies, including complete blood count, HIV enzyme-linked immunosorbent assay, erythrocyte sedimentation rate, and C-reactive protein, were unremarkable. Fundus angiography showed vitreous opacity in the right eye and a hypofluorescence lesion with hyperfluorescence margin in the peripheral retinal

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region in the early stage (Fig. 2).

The patient presented with immediate clinical symptoms including fever and headache. A lumbar puncture (LP) was conducted, and cerebrospinal fluid (CSF) analysis revealed the following results: nucleated cells 40 × 10^6/L, glucose 1.4 mmol/L, protein 2.04 g/L, and positive for cryptococcal antigen. The initial pressure was measured at 130 mmH2O and the CSF tested positive for cryptococcal antigen (titer 1:40) as shown in Table 1. Ink stain, Gram stain, and antacid stain yielded negative results, and macrogenetic gene sequencing did not detect any pathogenic microorganisms in the CSF. MRI findings indicated softening of the left basal ganglia radial crown infarct with glial hyperplasia and hemosiderosis deposition, consistent with cryptoencephalogenic findings (Fig. 3).

As a result, the patient was diagnosed with fungal endophthalmitis of the right eye, uveitis of the right eye, and cryptococcal meningoencephalitis. The patient received intravenous amphotericin B for three weeks, followed by a switch to oral fluconazole. During this time, oral 5-FC was also administered. However, the exudation of the choroidoretinal lesion worsened (Fig. 1B). Subsequently, the ophthalmologist performed vitrectomy, trans-scleral cryotherapy, and intravitreal injection (amphotericin B). One day after the surgery, a reduction in the size of the lesion was noted, with slight elevation of the surrounding retina and the presence of whiteish dots-like exudation along the vascular wall (Fig. 1C). During the last visit, which took place 6 months after the vitrectomy, gliosis and hyperpigmentation were observed in the original lesion, and the exudation along the vascular wall had been absorbed (Fig. 1D). The patient's final vision in the right eye was measured at 20/30. Throughout the course of the patient's illness, several cerebrospinal fluid and serological cryptococcal pathogenic tests were conducted (Table 1). The whole process of diagnosis and treatment of the patient is shown in Flowchart 1.

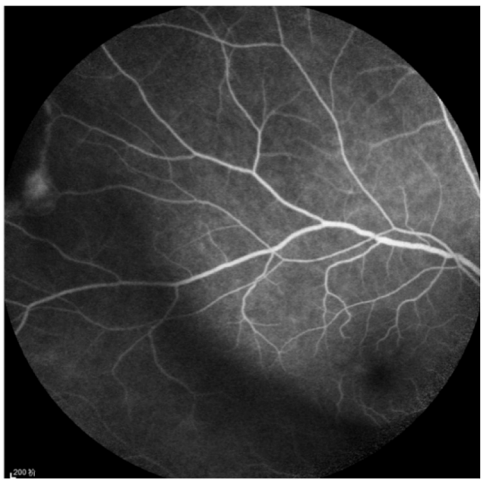


Fig. 2. Fundus fluorescence angiographic presentations of the right eye.

Discussion

Cryptococcal infections are primarily caused by Cryptococcus novelis, a microorganism commonly found in soil, decaying wood, or bird droppings. The main mode of transmission is through respiratory means. Our patient reported that her neighbor kept pigeons, which could have been the source of her illness. Despite significant advancements in antifungal and antiretroviral therapy, cryptococcal meningitis, the most common form of cryptococcosis, continues to have a high rate of illness and death worldwide. It remains a major clinical and economic burden in adults from many countries with a high prevalence of HIV [4]. Currently, only three classes of antifungal agents - polyenes, flucytosine, and azoles - are used to treat this fungal infection [5]. Given the limited availability of drugs, potential toxicity, and the risk of resistance development, there is an urgent need to either discover new antifungals or modify existing molecules with anticryptococcal activity.

The current study has identified four serotypes (A–D) within the C. neoformans and C. gattii species complexes, which have long been recognized. These serotypes can be distinguished by the polysaccharide that forms the capsule of these yeasts. With the increasing affordability of whole genome sequencing (WGS), researchers have sequenced genomes of C. neoformans and C. gattii strains recovered from endemic areas worldwide, as well as from sporadic cases. This sequencing has greatly contributed to our understanding of the origin, speciation, evolution, and diversification of these yeasts. Furthermore, it has enabled the identification of associations between genetic variants and virulence [6]. WGS has also facilitated the comparison of outbreak lineages, revealing various genetic differences such as mutations, deletions, transpositions, and recombination events. These differences may be related to habitat adaptation, virulence, and pathology [7,8]. These studies provide the opportunity to identify biomarkers, with the aim of detecting strains with specific tissue affinities for guiding clinical treatment and reducing patient mortality.

The members of the Cryptococcus neoformans and Cryptococcus gattii species complexes are the main etiological agents of cryptococcosis, a life-threatening fungal infection primarily affecting immunocompromised individuals, but also immunocompetent hosts or those with unknown risk factors [4]. C. neoformans causing endogenous endophthalmitis is rare, And the incidence was unknown [9]. Due to the limitations of current diagnostic techniques, clinicians may miss the diagnosis of fungal endophthalmitis, which has been reported in the literature in the past. The sensitivity of cerebrospinal fluid (CSF) cultures to detect Cryptococcus spp ranges from 50 % to 80 %. The sensitivity of antigen detection is up to 96 % [10]. Currently, there is limited literature reporting on the treatment of endophthalmitis caused by rare microorganisms. Therefore, early identification of pathogenic bacteria that infect patients with endophthalmitis is beneficial for clinical evaluation and prognosis prediction of patients.

Previous studies have shown that ocular complications of cryptococcal meningitis are more common in immunocompromised patients

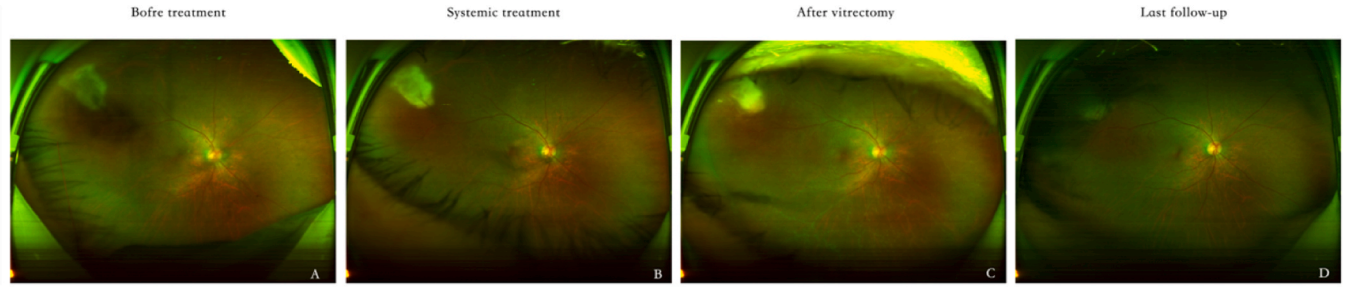


Fig. 1. Scanning laser ophthalmoscope (SLO). (A) Gray-white lesions in the supratemporal of retina in the first visit. (B) The exudation became severer after systemic anti-fungal treatment. (C) Shrinkage of the lesion one day after vitrectomy. (D) Gliosis and hyperpigmentation of the lesion in the last visit.

Table 1
Results of laboratory testing.

Projects	First admission	Second admission	Third admission	Fourth admission	Fifth admission
Date	December 2021	January 6,2022	January 17, 2022	April 2022	September 2022
Lumbar Puncture Cerebrospinal fluid pressure (mm H_2O)	130	145	125	100	130
Color	Clear	Clear	Clear	Clear	Clear
Cryptococcal antigen, titer	1:40	1:20	1:5	1:2	Negative
Nucleated cells ($\times 10^6$/L)	40	117	70	0	0
Protein (g/L)	2.04	1.67	1.08	0.63	0.46
Glucose (mmol/L)	1.4	2.7	2.81	3.56	3.85
Chlorine (mmol/L)	114	120	126	131	129
Serological Cryptococcal antigen titer	1:80	1:160	1:40	1:40	1:10

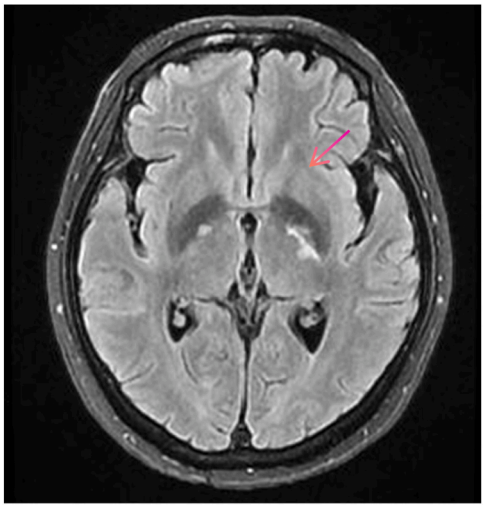


Fig. 3. A new cystic lesion is seen in the left basal ganglia area, and the lesion manifestations are consistent with cryptocerebral manifestations.

[11]. Two patterns of visual loss have been proposed: rapid and slow. Rapid visual loss occurs over hours and is often bilateral, severe, and permanent, with optic neuritis favored as the primary pathogenic mechanism [12,13]. In contrast, slow visual loss occurs over days, has a more favorable prognosis, and is thought to be secondary to the effects of intracranial hypertension and subarachnoid adhesions, and occurs more commonly in immunocompetent patients [12,13]. Our patient presents with progressive unilateral vision loss. Lumbar puncture suggests normal intracranial pressure and no subarachnoid problems on imaging. Thus, the patient's pattern of vision loss conforms to a slow-progressing pattern, which is consistent with previous studies [14]. Therefore, we suspect that the patient does not have ocular complications due to cryptococcal meningitis. In conjunction with the patient's ophthalmologic imaging, we consider the progressive decline in vision in the right eye of the patient to be the result of cryptococcal invasion of the eye. Finally, we performed cerebrospinal fluid examination and head MRI to confirm our conjecture, and auxiliary tests showed that the patient had CNS cryptococcal infection, which is rare in previous studies. Previous studies indicate that positive blood and CSF cryptococcal titers in the absence of disease should be regarded as early evidence of impending disseminated disease and/or meningitis [15].

In this case, our patient presented with a creamy yellow solitary chorioretinal lesion near the equator, accompanied by unilateral anterior segment inflammatory reaction. This particular sign can also be observed in cases of endophthalmitis caused by other microorganisms, leading to misdiagnosis and difficulties in treatment. Additionally, the patient exhibited signs of meningitis. According to the literature review, the predominant clinical presentation of cryptococcal endophthalmitis is often associated with meningitis, and may sometimes precede or follow the involvement of other anatomical sites. In our case, the presence of cryptococcal antigen in the patient's cerebrospinal fluid confirmed the suspicion of Cryptococcus infection. However, we were unable to detect cryptococcal presence in the vitreous sample. Previous reports suggest that while papilledema or optic nerve atrophy are considered ocular reactions to central nervous system infections, chorioretinitis could be a result of disseminated cryptococcosis in the choroidal circulation. Nevertheless, it remains unclear why our patient had only one solitary lesion in the right eye, instead of multiple lesions. In immunocompetent patients, 40 % (4/10) showed multiple lesions [16], whereas in HIV-infected patients, 50 % (10/20) suffered from disseminated cryptococcosis [17]. It appears that the immune status may play a minor role in controlling the dissemination of ocular cryptococcosis.

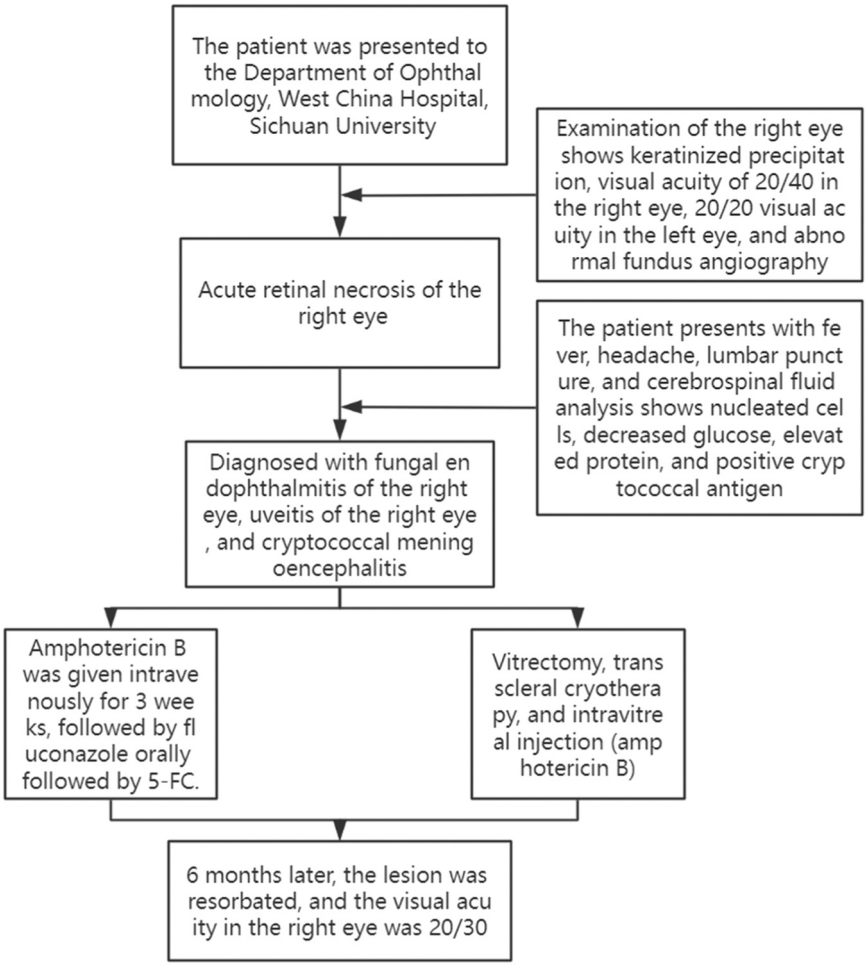
According to the management guidelines for cryptococcal disease proposed by the Infectious Diseases Society of America, it is recommended to extend the induction therapy of amphotericin-B plus fluconazole for 6 weeks and follow it with consolidation therapy of fluconazole for 8 weeks for immunocompetent patients. In this particular case, the signs of meningitis improved during the systemic treatment. However, the progression of chorioretinitis was not halted. As an adjunctive treatment, intravitreal amphotericin-B has been reported. Therefore, we performed vitrectomy and administered amphotericin-B intravitreally. This effectively controlled the chorioretinitis. Retinal angiography revealed hypofluorescence in the lesion and the surrounding vessels appeared to stop at the margin of the lesion, indicating poor perfusion within the lesion. The systemic medication may have difficulty reaching the center of the lesion. By injecting amphotericin-B intravitreally, it could directly target the cryptococcal infection.

Conclusions

To conclude, clinicians must keep in mind the potential for cryptococcal invasion of the eye when treating patients with progressive vision loss, even those who are immunocompetent. Luckily, our patient displayed neurological symptoms and was diagnosed with a confirmed cryptococcal infection, which was effectively treated with antifungal therapy. Previous research indicates that CSF and antigen testing may yield negative results in the early stages of cryptococcal infection [11], so it is important to repeat these tests for suspected cases.

Ethical approval

The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of the Sichuan University Biomedical Research Ethics Committee. Written informed consent was obtained from individual.



Flowchart 1. The whole process of diagnosis and treatment of the patient.

Consent

All authors and the guardian of patient agreed for the publication of this study.

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Author Statement

Guo Tang planned the study and wrote the manuscript. Hao Li analyzed the data. Chen Liang and Enqiang Chen provided critical comments/revisions of the manuscript. All authors commented on previous versions of the manuscript.

CRediT authorship contribution statement

Guo Tang: Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation, Conceptualization. **Hao Li:** Data curation. **Chen Liang:** Writing – review & editing, Writing – original draft. **Enqiang Chen:** Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability Statement

All data generated or analyzed during this study are included in this published article. In addition, other material and information on this case report are available from the corresponding author on reasonable request.

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Author Contributions

Guo Tang planned the study and wrote the manuscript. Hao Li analyzed the data. Chen Liang and Enqiang Chen provided critical comments/revisions of the manuscript. All authors commented on previous versions of the manuscript.

Institutional Review Board Statement

Not applicable. Informed Consent Statement: Informed consent was obtained from the subject involved in the study.

Conflicts of Interest

The authors declare no conflict of interest.

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