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Case Report

Case of cryptococcal choroiditis in adult with T-cell leukemia/lymphoma☆

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ABSTRACT

A rare case of 70-year-old woman with adult T-cell leukemia/lymphoma who developed multifocal choroiditis from a dissemination of *Cryptococcus neoformans* is reported. Ophthalmologic examination revealed multiple yellowish choroidal lesions in the posterior pole of both eyes. Sequential optical coherence tomographic images disclosed the involvement of the choroid and the consecutive changes in its architecture during the course of treatment. The recognition of these ocular manifestations may be important for the rapid diagnosis of *C. nerformans*-disseminated diseases. Rapid diagnosis and prompt therapy with intravitreal injection as well as systemic fosfluconazole and liposomal amphotericin B led to clinical improvement of intraocular cryptococcosis.

1. Introduction

Cryptococcus neoformans is an encapsulated fungus found worldwide in soil usually contaminated by avian excreta [1]. Infection occurs via inhalation and could be asymptomatic or later spread hematogenously from lung to other areas, in particular to the central nervous system [2]. Approximately 50% of patients who develop clinical disease have some evidence of underlying immunosuppression, such as a malignancy, human immunodeficiency virus infection, and connective tissue disorders [3–5].

The ocular involvements include papilledema, diplopia, nystagmus, sixth nerve palsy, ophthalmoplegia, ptosis, and optic atrophy. These ocular manifestations occur in approximately 40% of patients with cryptococcus meningitis and may represent a hematogenous dissemination or extension through the leptomeningitis [1,5,6]. Intraocular infection is rare and the reported manifestations include iridociliary granuloma, choroiditis, chorioretinitis, vitritis, endophthalmitis, exudative retinal detachments, and neuroretinitis [3–5,7–9].

We report a rare case of multifocal cryptococcal choroiditis with a serous retinal detachment. Sequential optical coherence tomographic images are reported for the first time and disclose the involvement of the choroid and the consecutive changes in its architecture during the course of treatment.

2. Case report

A 70-year-old Japanese woman was admitted to our hospital to treat her adult T-cell leukemia/lymphoma (ATLL). Because she also had hypoplastic bone marrow with poor systemic condition, a central venous catheter was implanted and systemic prednisolone (40 mg/day) was started. Fig. 1 showed the clinical manifestations, treatment, and time course.

On the14th day, she had a high fever and markedly elevated level of the serum C-reactive protein (11.0mg/dl, normal range is less than 0.3mg/dl). After obtaining blood cultures, treatment with antibiotics, cefepime (2g/day), was started.

On the 17th day, caspofungin (loading dose 70 mg, then 50 mg daily) was added to her treatment regimen. Because abnormal

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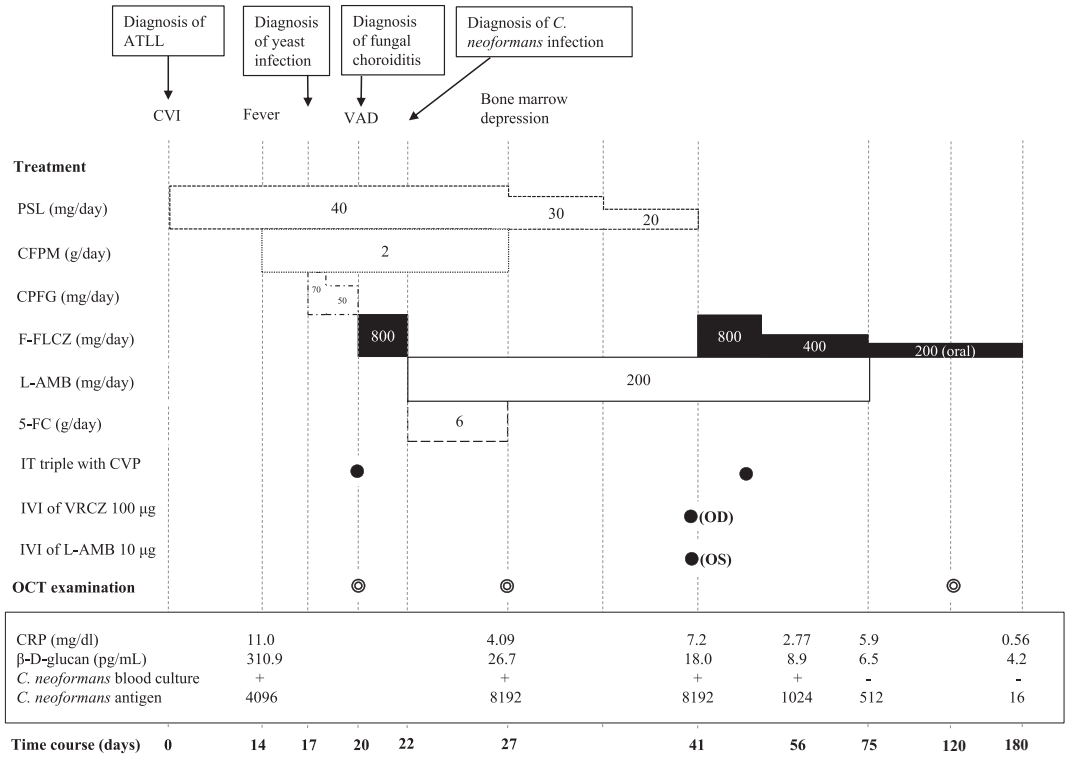

Fig. 1. The clinical manifestation, treatment, and time course. The clinical manifestation and diagnostic events are written at the top of the figure. Medical treatments are listed on the left-hand side and the continuation of each treatment is shown as a bar graph. The treatment administrated only once was shown as a black circle. Date of the OCT examination was marked as a double circle. Time course is written at the bottom. The levels of the serum C-reactive protein and the (1 → 3)-β-D-glucan, and the outcomes of the serum *C. neoformans* antigen test and the culture for *C. neoformans* are written along the time course. ATLL: adult T-cell leukemia/lymphoma, CVI: central venous catheter implantation, VAD: visual acuity deterioration, PSL: prednisolone, CFPM: cefepime, CPFG: caspofungin, F-FLCZ: fosfluconazole, L-AMB: liposomal amphotericin B, 5-FC: flucytosine, IT triple with CVP: intrathecal triple therapy with 50% dose of cyclophosphamide, vincristine, and prednisone, IVI: intravitreal injection, VRCZ: voriconazole, OD: right eye, OS: left eye, OCT: optical coherence tomography, CRP: level of the serum C-reactive protein, level of the serum (1 → 3)-β-D-glucan.

increase of the serum (1 → 3)-β-D-glucan (310.9 pg/mL, normal range is less than 11 pg/mL) and a yeast infection were detected in the blood which had been obtained on the 14th day. The serum *C. neoformans* antigen was higher than 1:4096. On the same day, she was referred to our Department of Ophthalmology because of suspicious fungal infection. The examination on the bed showed that her best-corrected visual acuity (BCVA) was 14/20 in the right eye (OD) and 16/20 in the left eye (OS). The intraocular pressure was 13 mmHg OD and 15 mmHg OS, and the pupils were round and reactive without an afferent pupillary defect. She had mild cataract in both eyes. There was no anterior chamber inflammation or anterior vitritis. There were no findings suggesting fungal endophthalmitis, although Roth spots that was thought to be caused by ATLL were observed in both eyes.

On the 20th day, intrathecal triple therapy with CVP (50% dose of cyclophosphamide, vincristine, and prednisone) for ATLL was administered following cerebrospinal fluid (CSF) collection for culture. Soon after the treatment, she reported an acute deterioration in her vision without headache or vomiting. The ophthalmic examinations on the same day showed that her BCVA was 8/20 OD and 4/20 OS. Slit-lamp examination revealed mild anterior chamber reaction in both eyes. Multiple yellow-white lesions and hemorrhages without papilledema were observed in the posterior pole, and a round, shallow serous macular detachment was present in both eyes (Fig. 2). Fluorescein angiography was not performed because of renal dysfunction and poor general condition. However, in OCT images, corresponding area of the serous retinal detachment showed the subretinal cystoid space separated by membranous structures and septa, and the chorioscleral border was blurred in both eyes (Fig. 2). The patient was diagnosed as having fungal infection in choroid and caspofungin was replaced by fosfluconazole (F-FLCZ, loading dose 800 mg) because of intraocular penetration (The treatment regimen at this point was prednisolone + cefepime + F-FLCZ).

Two days after CSF collection (on the 22nd day), budding yeasts were seen on an India ink preparation of the CSF. *C. neoformans* was recovered from cultures of the blood and CSF Investigations for other pathogens including cytomegalovirus, herpes simplex virus, varicella-zoster virus, toxoplasma, and *Mycobacterium tuberculosis* were negative. An x-ray of her chest and a CT scan of her head were normal. Based on the clinical findings, positive microscopic examination, and India ink test results, the patient was diagnosed with cryptococcal choroiditis. F-FLCZ was discontinued and intravenous administration of liposomal amphotericin B (L-AMB: 200 mg/day) and oral administration of flucytosine (6 g/day) were started (The treatment regimen was prednisolone + cefepime + L-AMB + flucytosine at this point). Her weight was 35 kg.

On the 27th day, five days after the introduction of L-AMB and flucytosine, the flucytosine had to be stopped because of bone marrow depression.

On the 41st day, after another two-week continuation of the L-AMB therapy, the choroidal lesions had little improved (Fig. 3), and the inflammation in the anterior segment had rather increased. Although OCT scans showed a decrease in the macular serous detachment, scans performed on yellow-white lesions revealed multiple bumps of the retinal pigment epithelium (RPE) with hyper-reflectivity substances within the bumps. There were focal thickening in the choroid with low reflectivity of the inner choroid.

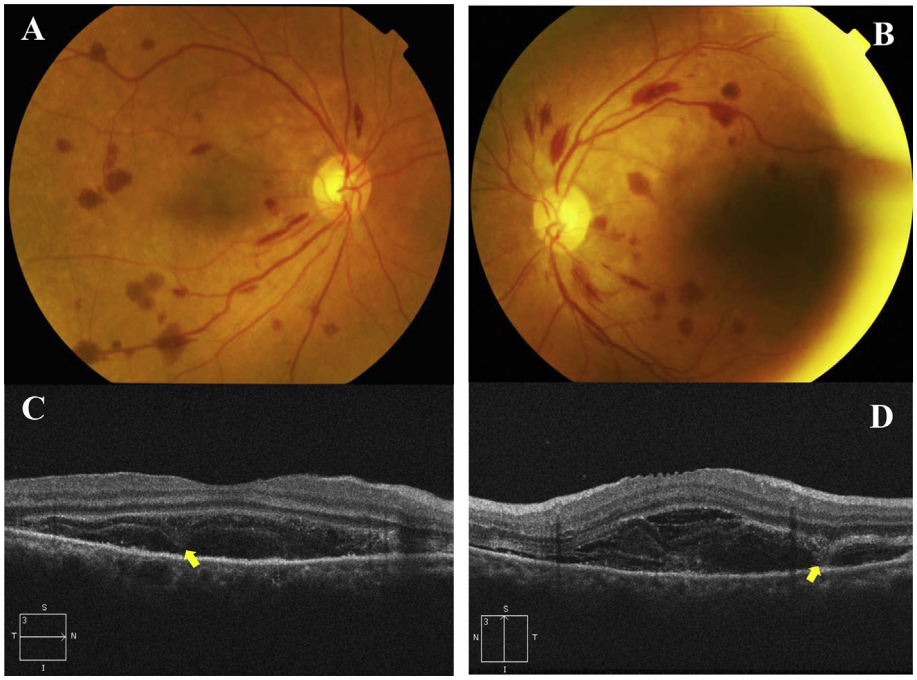

Fig. 2. Fundus photographs and optical coherence tomography (OCT) images in the right eye (left column) and left eye (right column) at the second consultation. Fundus photography shows multiple yellow-white lesions and hemorrhages in the posterior pole, and a serous macular detachment, without any papilledema in both eyes (A, B). In the OCT images, corresponding area of the serous retinal detachment shows the subretinal cystoid space separated by membranous structures and septa (yellow arrow) and the choriosclera border was unclear in both eyes (C, D).

In addition, the photoreceptor layer showed slight hyperreflectivity (Fig. 3). The serum *C. neoformans* antigen remained high and the blood culture remained positive at this point. Based on the results of antifungal susceptibility tests, systemic F-FLCZ (800mg/day for 7 days, then 400 mg daily) was added and intravitreal injection of antifungal agent was performed on both eyes (100 μg of Voriconazole OD and 10 μg of L-AMB OS).

On the 45th day, four days after beginning of the new treatment protocol (L-AMB + F-FLCZ + one intravitreal injection of antifungal agent), the choroidal lesions showed some resolution with hypopigmentation changes. Intrathecal triple therapy with CVP (50% dose of cyclophosphamide, vincristine, and prednisone) for ATLL was administered.

On the 75th day, after the four-week combination therapy of L-AMB and F-FLCZ, anterior inflammation and choroiditis gradually improved. The serum (1 → 3)-β-D-glucan level decreased to 6.5 pg/mL and the blood culture was negative. Intravenous L-AMB was discontinued and mogamulizumab was started for the ATLL. Intravenous administration of F-FLCZ was switched to oral FLCZ.

On the 120th day, her BCVA had improved to 12/20 OD and 10/20 OS. OCT scans showed a resolution of the macular serous detachment, however there was blurring of both interdigitation zone (IZ) and ellipsoid zone (EZ) except in the central foveal region. The RPE bumping and focal thickening of the choroid were decreased, but the reflectivity of the RPE bumps was increased (Fig. 4).

On the 180th day, administration of oral FLCZ was stopped because of impaired renal function. There was a resolution of the choroidal lesions and hemorrhages without recurrences, thereafter. Nevertheless, her condition deteriorated despite chemotherapy and treatment and she died for ATLL on the 240th day after hospitalization.

The cryptococcal strain isolated from the blood and CSF was identified as *C. neoformans* var. grubii by analyzing the sequences of the internal transcribed spacer regions [10]. Multi-locus sequence typing based on the sequence analysis of a set of polymorphic loci revealed that the isolate was molecular type ST5 [10].

The minimal inhibitory concentrations to amphotericin B, flucytosine, FLCZ, itraconazole, miconazole, micafungin, and VRCZ were 0.25, 4, 4, 0.06, 0.25, >16, and 0.06 μg/mL respectively.

This study was approved by the institutional review board and followed the tenets of the Declaration of Helsinki.

3. Discussion

We described a case of multifocal choroiditis caused by *C. neoformans* in a patient with ATLL. Ocular cryptococcosis is not very common, however, when present, it usually occurs in association with meningitis [5,11]. The *C. neoformans* reaches the eye from the meninges, via the optic nerve or blood stream [5,11]. Although our patient had positive results on India ink preparations and cultures of CSF samples, there were no other clinical signs of meningitis or its associated findings, such as papilledema, ophthalmoplegia, or ptosis.

There have been only a few reports which showed the serous retinal detachment related to *C. neoformans* infections [12]. A case of healthy male man who had cryptococcal meningitis with optic neuritis and atypical findings of serous retinal detachment was reported by Matsunaga and Iida [12]. The trigger for the serous retinal detachment in our case was unknown. However, there is a possibility that the ocular infection was not spread from the leptomeningeal sheath but hematogenously to the choroid. *C. neoformans* has been reported to cause granulomatous inflammation in the choriocapillaris and iridociliary capillaries [3,5,13], and subsequently, the inflammatory cells increase because of the choriocapillary permeability. These changes can then lead to the serous retinal detachment as in Vogt-Koyanagi-Harada disease [14]. In our case, the OCT scans at the early stage showed that choroiditis with a serous retinal detachment was present but inner retinal structure had been kept relatively. The septa may be fibrin

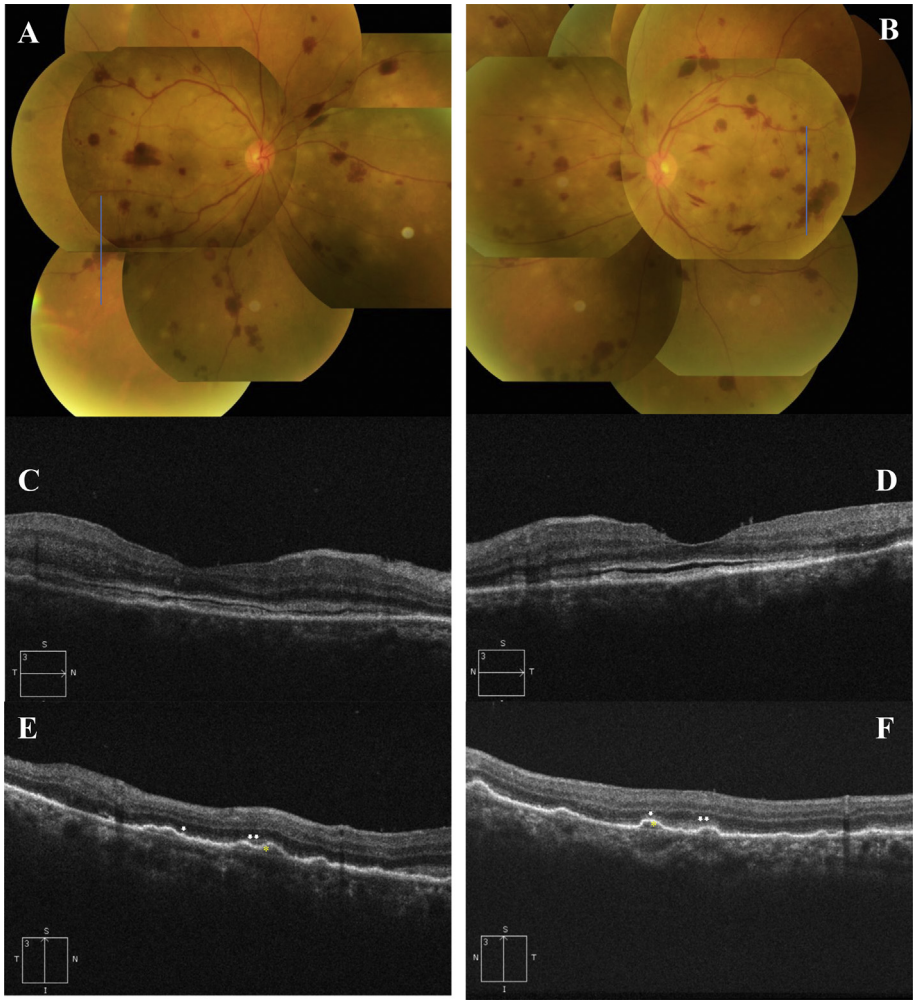

Fig. 3. Fundus photographs and optical coherence tomography (OCT) images in the right eye (left column) and left eye (right column) after 4-week treatment with antifungal agents. Fundus photography shows multiple yellowish choroidal lesions and hemorrhages. (A, B). In OCT images, the cystoid spaces and amount of the subretinal fluid were decreased (C, D), however, corresponding with yellow-white lesions, multiple bumps of the retinal pigment epithelium (RPE) with hyper-reflectivity substances inside (*) and with focal thickening of the choroid having low reflectivity of the inner choroid (white arrow), and a slight hyper-reflectivity at the level of photoreceptor layers were observed (E, F).

membranes, and the aggressive increase of fibrin may lead to exudative retinal detachment such as reported by Chen et al. [15].

Similar to the OCT image in a case with acquired immunodeficiency syndrome and cryptococcal choroiditis [11], the OCT scans in our case showed that the RPE was bumpy and the choroid beneath the yellow-white lesions was thickened. Histologic examination of the eyes with cryptococcal choroiditis in yellowish lesions confirmed the presence of *C neoformans* in the choroids [16,17]. A hyperrefractivity was visible at the level of the photo receptor layers in OCT images, which could be related to a secondary inflammation response to the underlying choroidal lesion [11] or a spread of the infection to the outer retinal layers. In spite of the resolution of the serous retinal detachment after treatment, impairments of IZ and EZ may be associated with the poor visual acuity at the late stage.

One of the most important diseases for differential diagnosis of cryptococcal choroiditis is other fungus endophthalmitis. Endogenous candida endophthalmitis is a sight-threatening disease, resulting from a hematogenous spreading of fungi to the eye [18]. The diagnosis in a patient with the disseminated *Candida* infection or significant risk factors is usually based on the identification of typical lesions, represented by multiple whitish fluffy balls floating in the vitreous [19]. Ocular candidiasis frequently follows an indolent course, progressing from chorioretinitis to vitritis and endophthalmitis [20]. Its showed peculiar features on OCT and two distinct patterns of chorioretinal involvement (intraretinal pattern and chorioretinal pattern) influencing the BCVA were identified [18].

In endogenous aspergillus, Adam CR et al. [21] demonstrated a diffusely thick choroid, predominantly subretinal exudation, and absence of retinal tissue disorganization on OCT images. In contrast to viral and protozoal retinitis, such as herpetic retinal necrosis, cytomegalovirus retinitis, and toxoplasmosis, *Aspergillus* spp. appears to produce a painful and predominantly choroidal infiltrations [22,23]. Rao NA et al. [24] compared candidasis with aspergillosis in clinical and histopathologic features and concluded that unlike *Candida* endophthalmitis, aspergillosis clinically presents with extensive areas of deep retinitis/choroiditis, and vitreous biopsy may not yield positive results. Histopathologically, it appears that *Aspergillus* grows preferentially along subretinal pigment epithelium and subretinal apace [24]. OCT allows a better visualization of lesions' localization without invasive histopathological procedures. These findings [11,15,18,21,22,24] including ours, suggest that analyzing OCT imaging at early stage may be helpful in differentiating fungal endophthalmitis caused by

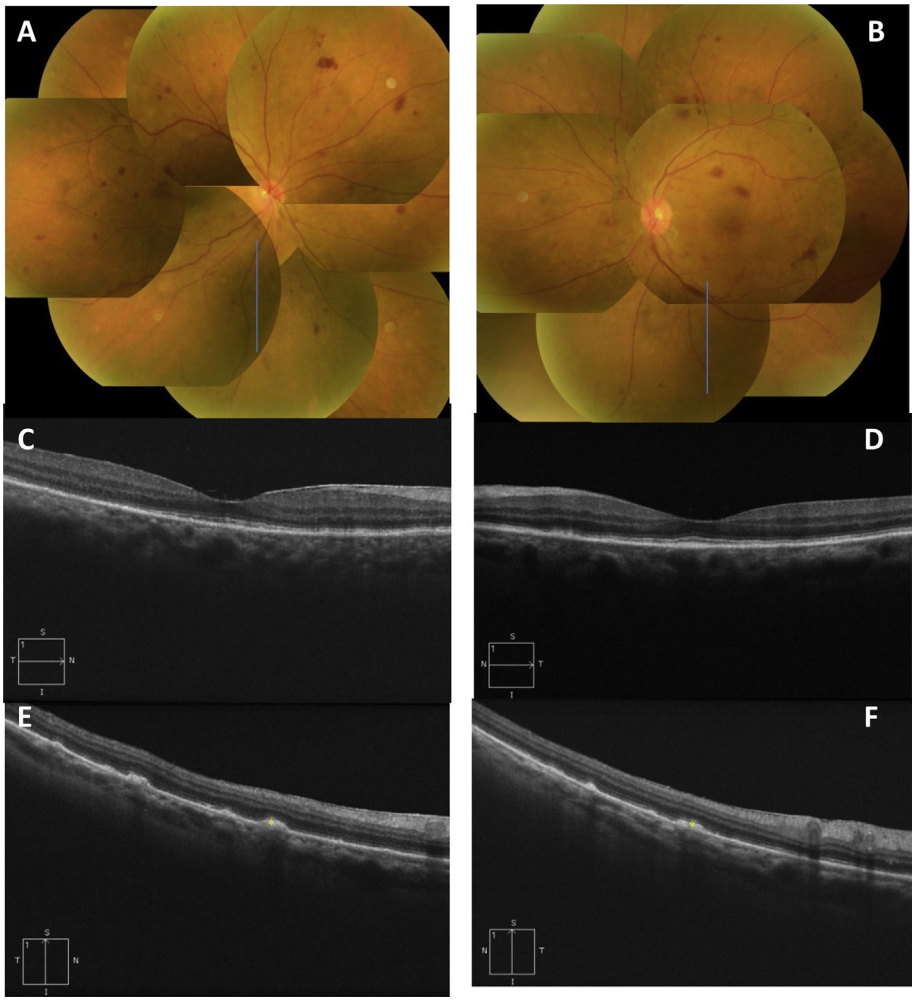

Fig. 4. Fundus photographs and optical coherence tomography (OCT) images in the right eye (left column) and left eye (right column) after 4-month treatment with antifungal agents. Fundus photography shows hypopigmentation of choroidal lesions and partial hemorrhage (A, B). OCT shows a resolution of serous retinal detachment and blurring of both interdigitation zone and ellipsoid zone (C, D). RPE humps and focal thickening in choroid are decreased. But the reflectivity inside the RPE humps (*) increases (E, F).

each organism, in which we cannot discriminate it with ophthalmoscopy.

β-D-glucan is considered to be useful for the screening of deep mycosis associated with fungal species such as *Candida*, *Aspergillus*, and *Fusarium* [25–27]. However, it's assay cannot be used to reliably diagnose certain infections including those caused by *Cryptococcus*, *Zygomycetes* such as *Mucor* and *Rhizopus, and Blastomyces* that either produce very low levels or do not produce β-D-glucan. The location of infection and presence of encapsulation may also affect the mount of β-D-glucan D-glucan produced [25–27]. Our patient showed elevated serum β-D-glucan levels. Obayashi T et al. [25] also reported the elevated serum β-D-glucan levels in patients of invasive fungal infections due to *Cryptococcus.* Although there may be a possibility to be false positive, it is considered to be related *Cryptococcus* infection in our case because those levels decreased with treatment (Fig. 1). Another possibility for the high serum β-D-glucan may be that β-D-glucan can readily seep out into the bloodstream as the mucinous capsule in our case was thinner than those of other *Cryptococcus* species. A positive β-D-glucan may support a prompt diagnostic, systemic workup, and initiation of antifungal therapy. However, false positive and negative reactions may occur, and it is necessary to fully characterize the utility of β-D-glucan testing in patients with fungal endophthalmitis.

The usual treatment of cryptococcal meningitis is a combination of intravenous L-AMB and oral flucytosine followed by a long course of oral FLCZ [28,29]. Since the optimal treatment of cryptococcal choroiditis has not been established, we used the treatment regimen for cryptococcal meningitis in our case. However, flucytosine had to be discontinued at an early stage because of bone marrow depression, and single L-AMB therapy did not improve the choroidal lesions. Alzaharani et al. recommended the treatment choice for cryptococcal infections. For systemic infection, amphotericin B is required intravenously with or without flucytosine, whereas for intraocular infection, intravitreal amphotericin B is needed as there is limited intraocular penetration [3]. Our patient was successfully treated with a combination of systemic F-FLCZ and L-AMB and intravitreal injection of VRCZ OD and L-AMB OS [30].

In conclusion, when cryptococcal meningitis is present, ophthalmic examinations including OCT are recommended. The OCT findings are helpful in the diagnosis and treatment by showing the involvement of the macula and choroid and the consecutive changes in those architectures in a case of intraocular cryptococcosis. Thus, the recognition of these ocular manifestations may be important for the rapid diagnosis of *C. nerformans*-disseminated diseases. Rapid diagnosis and prompt therapy with intravitreal injection as well as systemic F-FLCZ and L-AMB led to clinical improvement of intraocular cryptococcosis.

Conflicts of interest

None to declare.

The authors have no proprietary or financial interest in any products used in this study.

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