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Case Report

Multiple Intravitreal Liposomal Amphotericin B for a Case of *Candida glabrata* Endophthalmitis

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Keywords
Candida endophthalmitis · Fungal endophthalmitis · Ocular candidiasis · Intravitreal injection · Liposomal amphotericin B

Abstract
We report a case of *Candida glabrata* endophthalmitis which was effectively treated by intravitreal liposomal amphotericin B (L-AMB) injection. A 72-year-old man was referred to our department for positive blood culture of *Candida glabrata*. First ophthalmologic examination revealed a chorioretinal lesion in left eye, and the patient was diagnosed as possible candida chorioretinitis. Despite systemic antifungal therapy, his chorioretinal lesion increased in both eyes and complicated by vitritis. Intravitreal administration of L-AMB was introduced for probable candida endophthalmitis. Finally, improvement of vitritis and regression of chorioretinal lesions were obtained by total of 9 times intravitreal injection. Our case suggests the safety and efficacy of intravitreal L-AMB injection for *Candida glabrata* endophthalmitis.

Introduction

Endogenous fungal endophthalmitis (EFE) is a severe ocular condition which hematogenously disseminated due to systemic fungal infection. *Candida* species is the major pathogens of endogenous fungal endophthalmitis, known as ocular candidiasis (OC). Among the cases of OC, *Candida albicans* is the most prevalent pathogens. But other clinically important species including *Candida glabrata*, *Candida parapsilosis*, *Candida tropicalis*, and *Candida krusei* (non*albicans* species) also cause OC.

Two different pathways for intraocular dissemination of *Candida* have been proposed: through retinal and choroidal circulation. Optical coherence tomography (OCT) findings

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show different distribution of lesions from distinct pathways. That is, the retinal pathway corresponds to the lesions involving just inner sensory retina, whereas the choroidal pathway corresponds to the subretinal lesions [1]. The initial manifestation of OC is chorioretinitis, which subsequently extend to vitreous cavity. For diagnosis and classification of OC, the criteria described below were applied [2]. Proven endophthalmitis was defined as ocular lesions with positive cultures of vitreous humor. Probable endophthalmitis was defined as vitritis, including typically fluffy ball extending into vitreous cavity. Probable chorioretinitis was defined as deep, focal, and fluffy white lesions which restricted to chorioretinal layers. Possible chorioretinitis was defined as other nonspecific chorioretinal lesions including retinal hemorrhage, cotton-wool spots, or Roth spots.

The treatment of OC is principally systemic administration of antifungal drugs. However, when macular involvement and vitritis happen, intravitreal injection of antifungal drugs or vitrectomy should be taken into consideration [3]. Traditionally, amphotericin B (AMB) has been used as a first-line drug for intravitreal injection of antifungal drugs, but there are still concerns about retinal toxicity [4]. Recently, the usefulness of intravitreal injection of liposomal AMB (L-AMB), which has significantly improved systemic toxicity profile while retaining an antifungal effect compared to conventional AMB deoxycholate (AMB-D), for the treatment of OC caused by *Candida albicans* has been reported [5, 6]. However, there is no report of intravitreal L-AMB injection for the treatment of OC caused by *Candida glabrata*. Here, we report a case of *Candida glabrata* endophthalmitis which was effectively treated by intravitreal L-AMB injection.

Case Presentation

A 72-year-old man was referred to our department for positive blood culture of *Candida glabrata*. The patient underwent endoscopic hemoclip placement for small intestinal bleeding. He also underwent antibacterial therapy with vancomycin for blood infection of *Enterococcus faecium* at referral. He had well-controlled diabetes mellitus and CKD and presented acute kidney injury on CKD (serum Cr was 8.39 mg/dL [milligram per deciliter] at referral time). Antifungal therapy had already started with intravenous micafungin from 3 days before referral. He had no symptoms of vision.

First ophthalmologic examination performed 6 days after positive blood culture of *Candida glabrata* (from the date of collection). Slit-lamp examination showed no evidence of inflammation in the anterior chamber in both eyes. He had already undergone cataract surgery of both eyes about 5 years before initial visit, and there were no complications. Dilated fundus examination showed retinal hemorrhage and fine white spots in his posterior pole of both eyes. In addition to these findings, there was one white chorioretinal lesion besides optic disc in his left eye. We could not determine whether it is cotton-wool spot or infiltrate of fungal infection at that time. Therefore, our initial diagnosis was possible *Candida* chorioretinitis. Considering his renal dysfunction, we decided to continue intravenous micafungin with careful observation.

His systemic status improved with systemic antifungal therapy, and following blood culture revealed prompt negative conversion of *Candida glabrata*. But, his chorioretinal lesion gradually increased and became bilateral involvement at 1 week after initial examination (Fig. 1a, b). Therefore, antifungal therapy was switched to intravenous L-AMB with concern over inadequate intraocular penetration of micafungin. Despite systemic L-AMB administration, his chorioretinal lesions continued to progress and slit-lamp examination revealed vitreous cells at 2 weeks after the change of antifungal drugs (Fig. 1c, d). Based on the existence of vitritis, intravitreal L-AMB injection into both eyes (Table 1) was introduced

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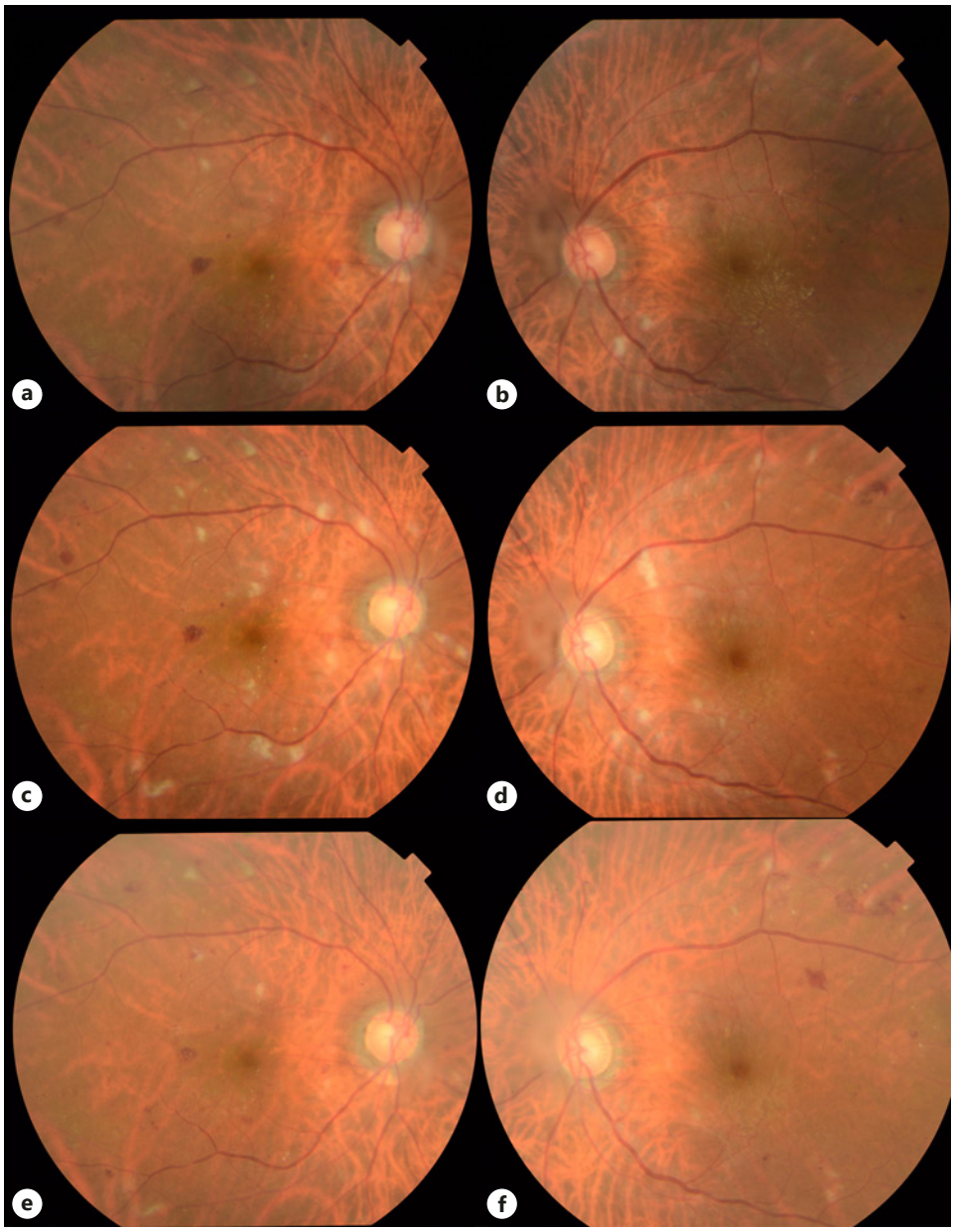

Fig. 1. Color fundus photograph findings in both eyes of our patient during follow-up period. First available color fundus images were taken 1 week after initial visit. **a**, **b** Typical fluffy infiltrates are shown in both eyes. **c**, **d** Despite intravenous L-AMB administration for 2 weeks (3 weeks after initial visit), the infiltrates progressed in both eyes. **e**, **f** After 9 times of intravitreal L-AMB injection, the number of points of infiltrates significantly decreased, and each of residual infiltrates seemed to be obsolete. L-AMB, liposomal amphotericin B.

for probable *Candida* endophthalmitis in addition to continuous intravenous L-AMB. Adequate informed consent was obtained from the patient after detailed information about potential risks and benefits of intravitreal L-AMB injection was given. At 9 weeks after introduction of intravitreal L-AMB administration, improvement of vitritis and regression of chorioretinal lesions were obtained by total of 9 times intravitreal injection to both eyes (Fig. 1e, f).

By using OCT, we observed an opalescent retinal lesion near the optic disc of his left eye over time. A horizontal OCT scan is taken immediately before the first intravitreal L-AMB

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Table 1. History of intravitreal injection into both eyes

The elapsed time since initial examination	Administration, *n*	Antifungal drugs	Dose	Concurrent systemic antifungal therapy
3 weeks	1	L-AMB	5 μg/0.1 mL	Intravenous L-AMB
4 weeks	2			
5 weeks	3			
6 weeks	4			
7 weeks	5			
8 weeks	6			
9 weeks	7			
10 weeks	8			
11 weeks	9		10 μg/0.1 mL	

L-AMB, liposomal amphotericin B.

administration revealed a highly reflective mass protruding from the inner retinal layers into the vitreous cavity (Fig. 2a). The lesion was restricted within the inner sensory retina, which suggested *Candida* spread via the retinal pathway in this case.

The lesions gradually shrank and eventually disappeared without a trace after the ninth intravitreal L-AMD administration (Fig. 2b–e). Then, both intravitreal and intravenous L-AMB was discontinued, and the patient was discharged. Renal function did not get worse after treatment for OC (serum Cr was 4.30 mg/dL at time of discharge). At 1 month after discharge, his best-corrected visual acuity was 20/20 OD and 20/16 OS, which remained almost unchanged from the first best-corrected visual acuity of 20/16 OD. Careful monitoring has confirmed no relapse of chorioretinal lesions so far. The impairment of visual acuity was not detected during the following period. Follow-up has been continued with a concern over long-term retinal toxicity of L-AMB.

Discussion/Conclusion

We experienced a case of *Candida glabrata* infection which eventually progressed to *Candida* endophthalmitis despite systemic antifungal therapy. OC caused by *Candida glabrata* was relatively rare clinical condition [7]. Generally, for the treatment of *Candida glabrata* infection, the systemic administration of echinocandins or AMB is used as a first-line drug because of the low sensitivity of triazoles for this species. But, in the case with OC, AMB tends to be used because of the poor intraocular penetration of echinocandins [2]. Even AMB, intravitreal injection is preferred because of inadequate intraocular penetration [8], but there are concerns about drug-induced retinal toxicity. Therefore, for OC caused by *Candida glabrata*, available antifungal drugs and their routes of administration are limited, and treatment may not be straightforward. We must keep in mind that OC caused by *Candida glabrata* needs careful monitoring and intensive care compared to other *Candida* species.

We used intravitreal administration of L-AMB for the treatment of *Candida glabrata* endophthalmitis refractory to systemic antifungal therapy. L-AMB is the earliest approved liposomal therapeutics. In this formulation, AMB is intercalated within the lipid bilayer of cholesterol-containing liposomes, which reduce its potential toxicity to human cells [9]. Whereas, AMB has higher binding affinity for ergosterol in fungal cell membranes compared with cholesterol, which enables L-AMB to retain the antifungal effect [10]. In addition, L-AMD demonstrates selective toxicity for fungal lesion because the vascular hyperpermeability caused by inflammation

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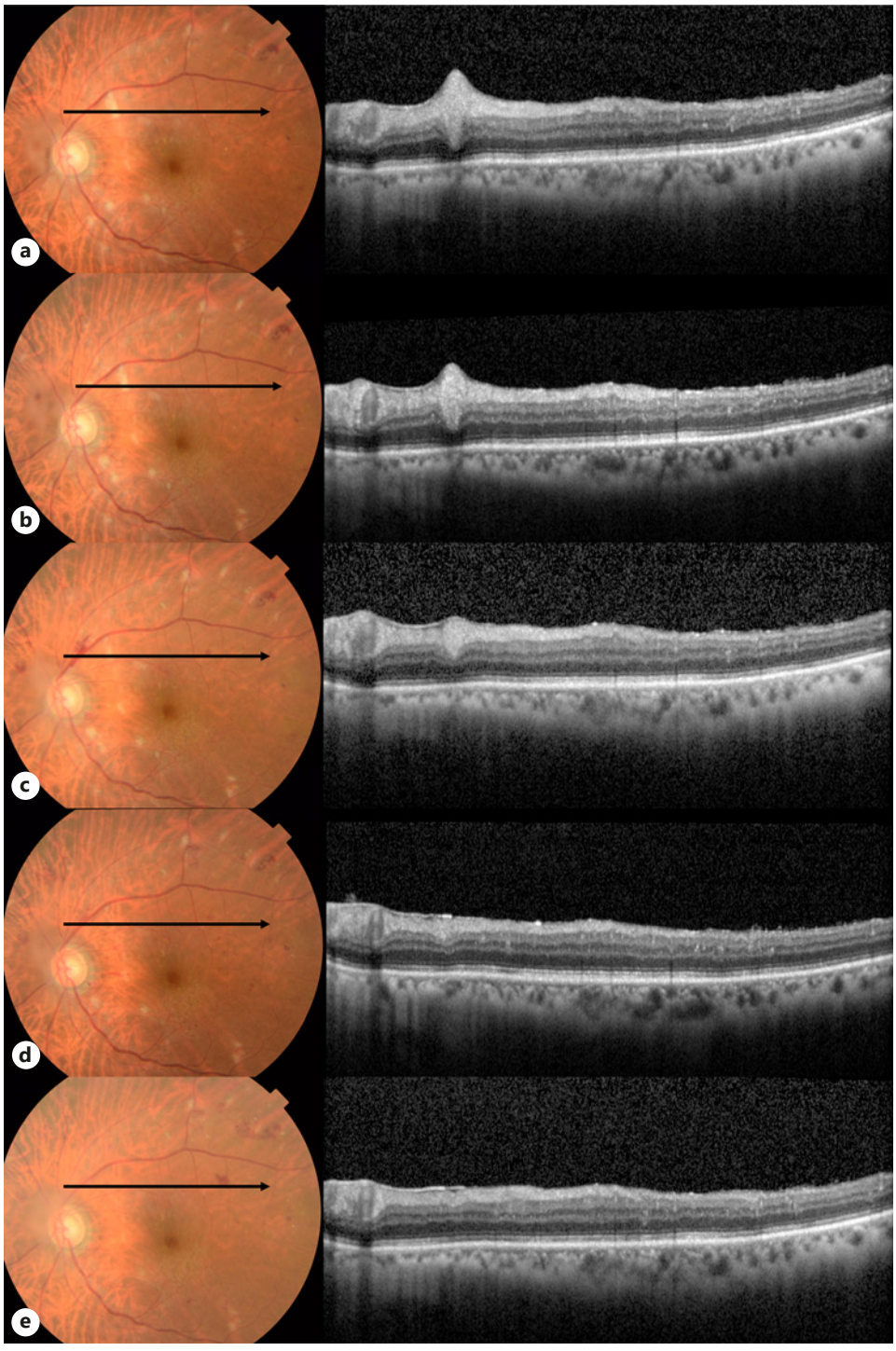

Fig. 2. Spectral-domain OCT findings in the left eye at the time just before introduction of intravitreal L-AMB administration (**a**), and after 1, 2, 4, and 9 times of intravitreal L-AMB administration (**b–e**) show that retinal infiltrations resolved in response to treatment. OCT, optical coherence tomography; L-AMB, liposomal amphotericin B.

facilitates the drug transfer to fungal lesions although extravascular permeation of L-AMB is limited because of its particle size of liposome in normal tissue. Based on these profiles, L-AMB can safely achieve higher concentrations in serum than conventional AMB-D [11].

Regarding intravitreal administration, the result of animal studies suggested that L-AMB had less ocular toxicity than AMB-D. Tremblay et al. [12] have compared the ocular toxicity of AMB-D with homemade L-AMB after intravitreal injection in rabbits. In their study, each of 40 eyes of healthy rabbits was randomly assigned to receive AMB-D or escalated doses of L-AMB (1, 5, 10, and 20 μg) or a vehicle. They reported that retinal damage was detected histologically in about one-third of eyes treated with AMB-D but none of eyes treated with L-AMB [12]. Barza et al. [13] intravitreally injected AMB-D (10, 20, and 30 μg) or homemade L-AMB (40, 80, and 120 μg) in 3 rhesus monkeys. They observed acute inflammation in the anterior chamber and vitreous cavity which tend to be left in the high-dose groups (30 μg of AMB-D or 120 μg of L-AMB) and described the possibility of L-AMB to reduce the ocular toxicity by at least fourfold [13]. With commercially available L-AMB, Cannon et al. [14] have compared the ocular toxicity of various doses of AMB-D, L-AMB, and AMB lipid complex (ABLC) that were intravitreal injected. Fifty-two eyes of healthy rabbits were randomly assigned to receive treatments including AMB-D, L-AMB, ABLC (in a dosage of 10, 20, 30, and 50 μg), and a vehicle. Ophthalmologic examinations found vitreal opacities or bands in none of the eyes treated with L-AMB, compared with 13 and 31% of the eyes treated with AMB-D and ABLC, respectively. On histologic examination, increasing grades of vitreal inflammation and retinal damage were detected along with increasing doses, but there was no significant difference among eyes with 3 different agents [14]. Koç et al. [5] reported clinical application of intravitreal L-AMB injection for the first time in 2010. They reported a case of bilateral *Candida albicans* endophthalmitis successfully treated with intravitreal 5 μg/0.1 mL L-AMB injection combined with vitrectomy in addition to systemic fluconazole therapy [5]. More recently, Bae and Lee [6] reported 7 eyes of 4 patients with *Candida albicans* endophthalmitis who successfully treated with intravitreal L-AMB injection alone or combined with vitrectomy. All patients also underwent concurrent systemic treatment of antifungal drugs. In their study, 7 eyes underwent intravitreal 10 μg/0.1 mL L-AMB, and 4 of those eyes underwent combination treatment with vitrectomy [6]. Any adverse effect was not detected in all reported cases. These reports suggest the safety and efficacy of the clinical application of intravitreal L-AMD injection for OC.

In our case, OC caused by *Candida glabrata* refractory to systemic antifungal therapy significantly improved by 9 times of weekly intravitreal injections of 5–10 μg/0.1 mL L-AMB. It is known that AMB has a long half-life in the vitreous humor. Wingard et al. [15] reported that the intraocular half-life of AMB-D was 7–15 days after intravitreal injection in nonvitrectomized rabbit eyes [15]. Tremblay et al. [12] reported that the clearance rate of AMB from the vitreous humor was similar for liposomal and nonliposomal preparations also in nonvitrectomized rabbit eyes [12]. We performed weekly intravitreal L-AMB injection in this case based on these evidences of pharmacokinetics. We started intravitreal L-AMB injection with the dose of 5 μg/0.1 mL since the vitritis was mild. After 8 times of intravitreal injection of 5 μg/0.1 mL L-AMB, the dose of the last injection was switched to 10 μg/0.1 mL in order to confirm whether the residual infiltrates leave room for further response to antifungal therapy. Any adverse effect has not been detected so far, which indicate multiple intravitreal injections of 5–10 μg/0.1 mL L-AMB is well tolerated. Though 1 case report, our case suggests that intravitreal L-AMB administration can be one of the effective options even for the treatment of OC caused by *Candida glabrata*. Further studies which include increased number of cases are needed to confirm the efficacy of clinical application of L-AMB as the drug for intravitreal administration. Moreover, validation of whether or not intravitreal administration of L-AMD with higher doses is safe is a considerable future task.

This is the first report of intravitreal L-AMB administration for the case of *Candida glabrata* endophthalmitis. Our case suggests the safety and efficacy of 5–10 μg/0.1 mL intravitreal L-AMB injection for *Candida glabrata* endophthalmitis.

Statement of Ethics

Consent to publish the case report was obtained. Moreover, this report does not contain any personal information that could lead to the identification of the patient in accordance with the Declaration of Helsinki.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

D. Sakai designed the concept of this work and drafted this manuscript. H. Imai and M. Nakamura critically reviewed the manuscript. All the authors read and approved the final manuscript.

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