Original Articles

Bibliographical Investigation (Domestic and Overseas) on the Treatment of Endogenous *Candida* Endophthalmitis over an 11-Year Period

Yukihiro Hamada¹, Ryota Okuma², Yusuke Katori¹, Saki Takahashi²,
Takeshi Hirayama^{1,2}, Yoshiaki Ichibe³, Masakazu Kuroyama^{1,2}

¹Department of Pharmacy, Kitasato University Hospital

²Kitasato University School of Pharmacy

³Department of Ophthalmology, Kitasato University School of Medicine

ABSTRACT

A bibliographic search was conducted of cases of *Candida* endophthalmitis reported in Japan and overseas between 2000 and 2011, in the Japana Centra Revuo Medicina Website of Japan Medical Abstracts Society (domestic reports) and MEDLINE (overseas reports). The investigation yielded 42 reports in domestic journals (49 cases; hereinafter referred to as domestic cases) and 39 reports in journals published overseas (46 cases; hereinafter referred to as overseas cases). The isolation rate of *Candida albicans* in the domestic cases was 65.3%, and that in the overseas cases was 71.7%. The initial treatment for the *Candida* endophthalmitis was fluconazole (FLCZ) therapy in 51.0% of the domestic cases and 38.1% of the overseas cases. Domestic reports suggested the effectiveness of FLCZ therapy for stage II cases, and of vitrectomy for stage III and IV cases. Reports from overseas, on the other hand, suggested the effectiveness of amphotericin B (AMPH-B) or voriconazole (VRCZ) therapy for stage II cases, and of vitrectomy for stage III and IV cases.

Key words : *Candida*, endophthalmitis, bibliographical investigation, fluconazole

Introduction

Endogenous *Candida* endophthalmitis is a complication associated with hematogenous dissemination of the causative *Candida* sp. Among the most commonly isolated pathogens is *C. albicans*, and FLCZ, which shows excellent intraocular transfer, has been used as the drug of first choice. However, recently, FLCZ-resistant strains of non-*albicans Candida* spp. or *C. albicans* are being reported at an increasing frequency¹⁾. In view of this and the recent clinical introduction of new anti-fungal drugs, which has expanded the scope of alternatives for the treatment of fungal infections, we conducted an investigation on the domestic trend for the treatment of endogenous

endophthalmitis²⁾. To date, however, there are only a few reports available on the trend of treatment for endogenous endophthalmitis. In this paper, we report our bibliographic investigation of *Candida* endophthalmitis covering the 11-year period from 2000-2011.

Methods

Cases reported between January 2000 and March 2011 were investigated by means of “and search” function in Japana Centra Revuo Medicina (domestic reports) using the Japanese key words corresponding to “*Candida*” and “endophthalmitis,” and MEDLINE (overseas reports) using the key words “*Candida*” and “endophthalmitis.” Subsequently, the authors conducted a

hand search of the reports thus identified.

In each of the papers/abstracts identified, we conducted a detailed assessment of the title, summary and main text and selected all reports containing data related to the classification criteria shown below and the treatment outcome. On the basis of the collected data, we analyzed the number of cases with *Candida* endophthalmitis, the *Candida* species isolated, the sites from which the *Candida* species were isolated, the underlying diseases, history/no history of catheter use, the drugs used for the treatment before and after the diagnosis of *Candida* endophthalmitis, course of treatment, disease stages according to Pittet's classification³⁾, and the treatment outcome by stage. The diagnosis was rated as "definite" in cases where *Candida* was isolated from the vitreous body/aqueous humor cultures, and as "clinical" in cases where the *Candida* was isolated from sites other than the eyes, or where the diagnosis of endophthalmitis was based on fundusoscopic findings and the serum β -D-glucan level.

The criteria for classification were: (I) Chorioretinal changes without extension to the vitreous cavity, (II) Fungal mass penetration through the inner limiting membrane and budding in the vitreous cavity, (III) Vitreous opacity resulting in unclear fundal observation, and (IV) Complication of retinal detachment with stage (III). In each case, success or failure of treatment was judged on the basis of improvement of the visual acuity. In cases where information on visual acuity was unavailable, treatment success/failure was judged on the basis of alleviation of the clinical symptoms of endophthalmitis or improvement of the serum β -glucan levels.

Because the treatment outcomes differed between the right and left eyes in some cases, the right and left eyes were counted separately in cases where both the eyes were affected by endophthalmitis. In the analysis of the treatment methods and outcomes and cases in which the treatment outcome remained unknown were excluded. Cases with exogenous endophthalmitis developing after ophthalmic surgery or trauma, cases in which the culture results remained unknown, cases with negative culture results or indeterminate pathogen, and cases that had been autopsied were also excluded.

In cases where 2 species of fungi were isolated,

analysis was conducted separately for both fungi.

The names of the drugs used have been abbreviated as follows: fluconazole (FLCZ), fos-fluconazole (F-FLCZ), micafungin (MCFG), amphotericin B (AMPH-B), liposomal amphotericin B (L-AMB), miconazole (MCZ), voriconazole (VRCZ), flucytosine (5-FC), caspofungin (CPFG).

Results

a) Number of papers investigated and their details

Search of the domestic literature published during the period covered by the study yielded 112 reports. After a detailed assessment of these reports, 42 reports were adopted for this study^{2, 4-44)}. The 42 adopted reports pertained to 49 cases, consisting of 31 males (63.3%) and 18 females (36.7%), with a mean age $\pm$ SD (minimum-maximum) of 62.9 ± 13.2 years (10-89) (Table 1). A search of the literature from overseas yielded 173 reports, of which 39 were adopted for this study⁴⁵⁻⁸³⁾. The 39 adopted reports pertained to 46 cases, consisting of 25 males (54.3%), 18 females (39.1%) and 3 individuals of unknown gender, with a mean age $\pm$ SD of 40.2 ± 19.7 years (0-83) (Table 2). Of the 95 cases (domestic + overseas), 91 cases (49 domestic and 42 overseas cases) not falling under any of the exclusion criteria were included for this analysis.

b) Underlying diseases and risk factors

In the analysis of the background variables among the patients surveyed, the underlying diseases identified in the domestic cases were malignant tumor (18 cases), diabetes mellitus (14 cases), gastrointestinal disease (11 cases), infection (6 cases), urological disease (4 cases), and unknown (no information available; 2 cases). The risk factors identified in the domestic cases were IVH insertion (37 cases), diabetes mellitus (14 cases), recent surgery (7 cases), chemotherapy (7 cases), steroid therapy (3 cases), antimicrobial drug therapy (2 cases), and unknown (no information available; 2 cases) (Table 1). The underlying diseases identified in the overseas cases were: malignant tumor (12 cases), diabetes mellitus (6 cases), infection (5 cases), gastrointestinal disease (4 cases), hepatitis C (3 cases), AIDS (2 cases), and unknown (no information available; 5 cases). The risk factors identified in the overseas cases were IVH insertion (14 cases),

Table 1. Reported cases *Candida* endophthalmitis in Japan

	Year	Author	Age	Gender	Underlying disease	Risk	Catheter use	Species	Treatment before diagnosis	Diagnostic vitrectomy	Treatment after diagnosis
1	2011	Hamada et al. ²⁾	64	F	multiple system atrophy, diabetes	diabetes, IVH*	+	<i>C.tropicalis</i>	MCFG	-	MCFG → VRCZ → L-AMB
2	2010	Fujiwara et al. ⁴⁾	58	F	diabetes	diabetes	-	<i>C.glabrata</i>	-	-	MCFG
3	2010	Nakamura et al. ⁵⁾	60	F	diabetes	diabetes	unknown	<i>C.glabrata</i>	-	-	MCFG
4	2010	Harada et al. ⁶⁾	55	M	maxillofacial injury	IVH	+	<i>C.albicans</i>	MCFG	-	F-FLCZ → VRCZ → FLCZ
5	2009	Zhenyu et al. ⁷⁾	63	M	bowel perforation	IVH, after surgery	+	<i>C.albicans</i>	MCFG	-	VRCZ → Vitrectomy
6	2009	Fujii et al. ⁸⁾	51	F	diabetes	diabetes	-	<i>C.albicans</i>	-	-	FLCZ → Vitrectomy
7	2009	Ishizaki et al. ⁹⁾	59	M	ulcerative colitis	prednisolone	-	<i>C.albicans</i>	-	-	F-FLCZ
8	2009	Itami et al. ¹⁰⁾	75	M	myelodysplastic syndrome	chemotherapy	unknown	Non- <i>albicans</i>	MCFG	-	L-AMB
9	2009	Seto et al. ¹¹⁾	73	F	tongue cancer	IVH	+	<i>C.albicans</i>	-	-	FLCZ
10	2008	Hosokawa et al. ¹²⁾	71	M	bile duct cancer	IVH	+	Non- <i>albicans</i>	F-FLCZ	-	F-FLCZ (increase) → VRCZ
11	2008	Nakanishi et al. ¹³⁾	63	F	kidney stones	-	-	<i>Candida.sp</i>	-	-	F-FLCZ → FLCZ → Vitrectomy
12	2008	Nomura et al. ¹⁴⁾	38	F	tongue cancer	IVH, administration of antimicrobial agent	+	<i>C.albicans</i>	MCFG	-	FLCZ
13	2008	Okubo et al. ¹⁵⁾	54	M	hepatic abscess peritonitis, diabetes	IVH, diabetes	+	<i>C.albicans</i>	-	-	FLCZ → Vitrectomy
14	2007	Nakai et al. ¹⁶⁾	70	F	large bowel perforation	IVH	+	<i>C.albicans</i>	MCFG	-	F-FLCZ → MCFG
15	2007	Onozawa et al. ¹⁷⁾	58	M	mouth cancer	IVH	+	<i>C.albicans</i>	-	-	FLCZ → VRCZ → Vitrectomy
16	2007	Tamaki et al. ¹⁸⁾	52	F	ulcerative colitis	IVH	+	<i>C.albicans</i>	-	-	FLCZ → Vitrectomy
17	2007	Tamaki et al. ¹⁸⁾	71	M	lung cancer	IVH, chemotherapy	+	<i>C.albicans</i>	FLCZ	-	Vitrectomy
18	2007	Tamaki et al. ¹⁸⁾	59	M	interstitial pneumonia	IVH	+	<i>C.albicans</i>	FLCZ	-	Vitrectomy
19	2006	Itano et al. ¹⁹⁾	63	F	urolithiasis	-	-	<i>Candida.sp</i>	-	-	FLCZ → Vitrectomy
20	2006	Iwamoto et al. ²⁰⁾	70	F	sigmoid colon cancer	IVH, after surgery	+	<i>Candida.sp</i>	-	-	FLCZ → Vitrectomy
21	2006	Oh et al. ²¹⁾	62	M	infection, diabetes	diabetes	-	<i>Candida.sp</i>	-	-	FLCZ
22	2006	Toshikuni et al. ²²⁾	69	M	urolithiasis	IVH	+	<i>C.albicans</i>	FLCZ → MCFG	-	MCFG
23	2005	Miyaki et al. ²³⁾	68	M	rectal cancer, diabetes	IVH, after surgery, diabetes	+	<i>C.albicans</i>	-	-	MCZ + FLCZ
24	2005	Miyamura et al. ²⁴⁾	75	F	pancreas cancer	IVH	+	<i>C.albicans</i>	-	-	FLCZ
25	2005	Oikawa et al. ²⁵⁾	89	M	urolithiasis, diabetes	diabetes	-	<i>C.albicans</i>	MCFG	-	FLCZ → Vitrectomy
26	2005	Watanuki et al. ²⁶⁾	68	F	upper gingival cancer	IVH, chemotherapy	+	<i>C.albicans</i>	-	-	FLCZ
27	2004	Arroyo JG et al. ²⁷⁾	43	M	infectious central venous thrombosis, diabetes	diabetes	-	<i>C.albicans</i>	FLCZ + 5-FC + AMPH-B	-	AMPH-B → Vitrectomy
28	2004	Mochizuki et al. ²⁸⁾	72	F	gastric cancer	IVH, after surgery	+	<i>C.albicans</i>	FLCZ	-	MCFG
29	2004	Mochizuki et al. ²⁸⁾	76	M	gastric cancer	IVH, after surgery	+	<i>C.albicans</i>	FLCZ	-	MCFG
30	2004	Mochizuki et al. ²⁸⁾	75	M	ulcerative colitis	IVH	+	<i>C.glabrata</i>	MCFG	-	MCFG + MCZ
31	2004	Sounou et al. ²⁹⁾	54	M	acute myelogenous leukemia	IVH, chemotherapy	+	<i>C.albicans</i>	MCFG	-	MCFG → F-FLCZ

32	2003	Fujiwara et al. ³⁰⁾	82	F	-	IVH	+	<i>C.albicans</i>	-	-	FLCZ → Vitrectomy
33	2003	Honda et al. ³¹⁾	57	M	-	IVH, malnutrition	+	<i>C.albicans</i> <i>C.parapsilosis</i>	FLCZ	-	AMPH-B → Vitrectomy
34	2003	Kameya et al. ³²⁾	42	M	gastrointestinal bleeding, diabetes	IVH, diabetes	+	<i>Candida.sp</i>	FLCZ	-	FLCZ → AMPH-B
35	2002	Hatanaka et al. ³³⁾	50	M	abdominal leiomyosarcoma	IVH, chemotherapy	+	<i>C.albicans</i>	FLCZ	-	MCZ + 5-FC
36	2002	Kobayashi et al. ³⁴⁾	71	M	intramuscular abscess, diabetes	IVH, prednisolone, diabetes	+	<i>C.albicans</i>	-	-	FLCZ
37	2002	Sakata et al. ³⁵⁾	66	M	gastric cancer, rectal cancer	IVH	+	<i>C.albicans</i>	-	-	FLCZ → AMPH-B
38	2002	Sakata et al. ³⁵⁾	59	M	duodenal perforation	IVH	+	<i>C.albicans</i>	FLCZ	-	FLCZ (increase) → AMPH-B
39	2002	Sakata et al. ³⁵⁾	71	M	Churg-strauss syndrome	IVH, prednisolone	+	<i>C.albicans</i>	FLCZ	-	FLCZ (increase) → AMPH-B
40	2002	Yakusigawa et al. ³⁶⁾	74	M	gastric cancer, diabetes	IVH, diabetes	+	<i>C.albicans</i>	FLCZ	-	FLCZ (increase)
41	2001	Takasima et al. ³⁷⁾	50	M	perianal abscess, diabetes	IVH, diabetes	+	<i>C.albicans</i>	FLCZ	-	FLCZ
42	2001	Minamino et al. ³⁸⁾	74	M	non-Hodgkin's lymphoma	IVH, chemotherapy	+	<i>C.albicans</i>	-	+	Vitrectomy → FLCZ
43	2001	Torisaki et al. ³⁹⁾	10	F	acute myelogenous leukemia	IVH, chemotherapy	+	<i>Candida.sp</i>	FLCZ	-	FLCZ (increase)
44	2000	Iida et al. ⁴⁰⁾	73	M	esophagitis, diabetes	diabetes	unknown	<i>Candida.sp</i>	-	-	FLCZ
45	2000	Iida et al. ⁴⁰⁾	84	M	lumbar vertebra fracture, psoriasis	administration of immunosuppressants, administration of antimicrobial agent	unknown	<i>Candida.sp</i>	-	-	FLCZ
46	2000	Kawase et al. ⁴¹⁾	61	F	ileus	IVH	+	<i>Candida.sp</i>	-	-	FLCZ → Vitrectomy
47	2000	Kohtani et al. ⁴²⁾	72	F	sigmoid colon cancer	IVH, after surgery	+	<i>Candida.sp</i>	-	-	FLCZ
48	2000	Kumada et al. ⁴³⁾	54	M	ileus	IVH, after surgery	+	<i>C.tropicalis</i>	FLCZ	-	FLCZ (increase) → Vitrectomy
49	2000	Ota et al. ⁴⁴⁾	57	M	infection	IVH	+	<i>C.albicans</i>	FLCZ	-	MCZ

*IVH: Intravenous Hyperalimentation

recent surgery (8 cases), diabetes mellitus (6 cases), drug abuse (6 cases), chemotherapy (4 cases), antimicrobial drug therapy (3 cases), steroid therapy (2 cases), AIDS (2 cases), and unknown (no information available; 9 cases) (Table 2).

c) Isolated *Candida* species

The *Candida* species isolated from the blood, catheter tip, vitreous body, etc., of the 49 domestic cases (including 1 case from which 2 species of *Candida* were isolated) were *C. albicans* (32 cases), *C. glabrata* (3 cases), *C. tropicalis* (2 cases), *C. parapsilosis* (1 case), Non-*albicans Candida* (2 cases), and other *Candida* sp. (10 cases) (Fig. 1). *Candida* species isolated from the 46 overseas cases (including 1 case from which 2 species of *Candida* were isolated) were *C. albi-*

cans (33 cases), *C. glabrata* (3 cases), *C. tropicalis* (2 cases), *C. krusei* (2 cases), *C. parapsilosis* (1 case), and other *Candida* sp. (6 cases) (Fig. 2).

Table 3 and 4 show the sites from which the *Candida* species were isolated and the types of *Candida* isolated. Among the 49 cases from Japan, vitreous body/aqueous humor culture was conducted in 11 (22.4%), blood culture in 26 (53.1%), catheter culture in 18 (36.7%), and urine culture in 8 (16.3%). Among the 46 cases from overseas, vitreous body/aqueous humor culture was conducted in 21 (45.7%), blood culture in 29 (63.0%), catheter culture in 4 (8.7%) and urine culture in 3 (6.5%).

In the analysis of the types of *Candida* isolated from each site, *C. albicans* was isolated in all the 4 of the 4 vitreous body culture-positive cases reported from Japan. Among the overseas cases,

Table 2. Reported cases *Candida* endophthalmitis in overseas

	Year	Author	Age	Gender	Underlying disease	Risk	Catheter use	Species	Treatment before diagnosis	Diagnostic vitrectomy	Treatment after diagnosis
1	2010	Muzaliha MN et al. ⁴⁵⁾	63	M	diabetes, fatty liver	diabetes, prednisolone	-	<i>C.glabrata</i>	-	-	AMPH-B
2	2009	Bernbeck B et al. ⁴⁶⁾	15	M	acute myelogenous leukemia	chemotherapy	-	<i>C.krusei</i>	AMPH-B	-	AMPH-B + 5-FC
3	2009	Ozdek S et al. ⁴⁷⁾	61	F	pancreatic cancer	after surgery, chemotherapy	+	<i>C.albicans</i>	FLCZ	-	FLCZ
4	2009	Biju R et al. ⁴⁸⁾	73	M	chronic renal failure, diabetes	IVH*, prednisolone, diabetes	+	<i>Candida.sp</i>	-	-	VRCZ
5	2009	Oliva AM et al. ⁴⁹⁾	43	M	oral thrush	-	+	<i>C.albicans</i>	-	+	Vitrectomy → VRCZ → FLCZ → MCFG
6	2009	Ha J et al. ⁵⁰⁾	1	M	burn	burn	+	<i>C.albicans</i> <i>C.parapsilosis</i>	AMPH-B	-	AMPH-B
7	2007	Najimi NG et al. ⁵¹⁾	83	M	urinary-tract infection	-	-	<i>C.albicans</i>	FLCZ	-	FLCZ (increase) → Vitrectomy
8	2007	Albini TA et al. ⁵²⁾	34	M	hepatitis C	drug abuse	-	<i>C.albicans</i>	-	+	Vitrectomy
9	2007	Albini TA et al. ⁵²⁾	37	M	AIDS	drug abuse, AIDS	unknown	<i>C.albicans</i>	-	+	Vitrectomy
10	2007	Tedeschi M et al. ⁵³⁾	28	F	toxemia of pregnancy	IVH	+	<i>C.albicans</i>	-	-	FLCZ
11	2007	Gunasekerav et al. ⁵⁴⁾	73	F	colon cancer	IVH, after surgery	unknown	<i>C.albicans</i>	-	-	FLCZ → ITCZ
12	2006	Osthoff M et al. ⁵⁵⁾	52	F	duodenal ulcer	IVH, after surgery	+	<i>C.albicans</i>	-	-	Vitrectomy
13	2006	Trpin S et al. ⁵⁶⁾	31	F	hepatitis C	drug abuse	unknown	<i>C.albicans</i>	-	-	FLCZ
14	2006	Hakki M et al. ⁵⁷⁾	35	F	acute myelogenous leukemia	chemotherapy	unknown	<i>C.krusei</i>	CPFG	-	L-AMB → VRCZ
15	2006	Rothe C et al. ⁵⁸⁾	45	M	rectal cancer	after surgery	-	<i>C.albicans</i>	-	-	FLCZ
16	2006	Williams MA et al. ⁵⁹⁾	32	F	-	-	-	<i>Candida.sp</i>	-	-	FLCZ → Vitrectomy
17	2005	Gauthier GM et al. ⁶⁰⁾	33	M	testicular cancer	IVH, after surgery	+	<i>C.albicans</i>	-	-	CPFG
18	2005	Jang GJ et al. ⁶¹⁾	63	F	acute necrotizing pancreatitis	IVH, administration of antimicrobial agent	+	<i>Candida.sp</i>	VRCZ	-	VRCZ
19	2005	Vianna RN et al. ⁶²⁾	35	M	-	-	-	<i>C.albicans</i>	-	-	AMPH-B → VRCZ
20	2005	Sarria JC et al. ⁶³⁾	39	M	peritonitis	IVH, after surgery	+	<i>C.glabrata</i>	-	-	CPFG
21	2005	Breit SM et al. ⁶⁴⁾	66	F	colon cancer	-	unknown	<i>C.glabrata</i>	FLCZ	-	VRCZ + CPFG
22	2005	Breit SM et al. ⁶⁴⁾	42	M	endocarditis	drug abuse	unknown	<i>C.albicans</i>	FLCZ	-	VRCZ + CPFG
23	2005	Breit SM et al. ⁶⁴⁾	48	F	lung cancer, ovarian cancer	IVH, malnutrition	+	<i>C.albicans</i>	FLCZ	-	VRCZ
24	2005	Breit SM et al. ⁶⁴⁾	48	F	ileus	IVH	+	<i>C.albicans</i>	unknown	-	VRCZ + CPFG → AMPH-B
25	2005	Breit SM et al. ⁶⁴⁾	52	M	T-cell lymphoma	-	unknown	<i>C.albicans</i>	-	-	VRCZ
26	2003	Kusaka S et al. ⁶⁵⁾	53	F	thyroid tumor	IVH, after surgery	+	<i>C.albicans</i>	unknown	-	FLCZ
27	2002	Chang TS et al. ⁶⁶⁾	24	F	abortion	abortion	unknown	<i>C.albicans</i>	-	-	Vitrectomy + AMPH-B
28	2002	Feman SS et al. ⁶⁷⁾	46	M	diabetes	diabetes	unknown	<i>C.albicans</i>	FLCZ	-	AMPH-B + 5-FC
29	2002	Tsai CC et al. ⁶⁸⁾	33	F	infectious chorioamnionitis	-	unknown	<i>C.albicans</i>	FLCZ	-	FLCZ → Vitrectomy
30	2002	Recchia FM et al. ⁶⁹⁾	26	F	anorexic	IVH	+	<i>C.albicans</i>	AMPH-B	-	AMPH-B
31	2002	Recchia FM et al. ⁶⁹⁾	30	M	infection	IVH, administration of antimicrobial agent	+	<i>C.albicans</i>	-	-	FLCZ → Vitrectomy

32	2002	Recchia FM et al. ⁶⁹⁾	60	M	prostate cancer, diabetes	after surgery, diabetes	unknown	<i>Candida.sp</i>	-	-	FLCZ → Vitrectomy
33	2002	Alexandridou A et al. ⁷⁰⁾	40	M	tattoo	-	unknown	<i>C.albicans</i>	-	-	AMPH-B + FLCZ
34	2002	Montha VV et al. ⁷¹⁾	44	M	deep venous thrombosis	IVH	+	<i>Candida.sp</i>	-	-	FLCZ → Vitrectomy
35	2001	Mialhes P et al. ⁷²⁾	31	M	AIDS	AIDS, administration of antimicrobial agent	unknown	<i>C.albicans</i>	FLCZ	-	FLCZ → AMPH-B → Vitrectomy
36	2001	Kou HK et al. ⁷³⁾	59	F	urinary-tract infection, diabetes	diabetes	unknown	<i>C.albicans</i>	FLCZ	-	FLCZ
37	2001	Pinna A et al. ⁷⁴⁾	27	M	hepatitis C	drug abuse	unknown	<i>C.albicans</i>	-	+	Vitrectomy → AMPH-B
38	2001	Ko YC et al. ⁷⁵⁾	55	M	diabetes	diabetes	unknown	<i>C.albicans</i>	-	-	FLCZ
39	2001	Stern JH et al. ⁷⁶⁾	0	F	low birth weight infant	low birth weight infant	unknown	<i>C.albicans</i>	-	+	Vitrectomy → AMPH-B → FLCZ
40	2001	Vose M et al. ⁷⁷⁾	16	M	Crohn disease	IVH	+	<i>C.albicans</i>	FLCZ	-	FLCZ → Vitrectomy
41	2000	Klein A et al. ⁷⁸⁾	42	M	-	drug abuse	unknown	<i>C.albicans</i>	-	-	Vitrectomy
42	2000	Todd Johnston W et al. ⁷⁹⁾	0	un-known	low birth weight infant	low birth weight infant	unknown	<i>C.albicans</i>	AMPH-B + 5-FC	-	AMPH-B + 5-FC
43	2005	Gualino O et al. ⁸⁰⁾	50	F	breast cancer	chemotherapy	unknown	<i>Candida.sp</i>	unknown	unknown	unknown
44	2005	Dotto Pde F et al. ⁸¹⁾	0	M	sepsis	low birth weight infant	unknown	<i>C.albicans</i>	unknown	unknown	unknown
45	2009	Geirsdóttir A et al. ⁸²⁾	un-known	un-known	unknown	unknown	unknown	<i>C.tropicalis</i>	unknown	unknown	unknown
46	2008	Richter JC et al. ⁸³⁾	un-known	un-known	unknown	unknown	unknown	<i>C.tropicalis</i>	unknown	unknown	unknown

*IVH: intravenous hyperalimentation

Fig. 1. The isolation rate of *Candida* species in the domestic cases.

Fig. 2. The isolation rate of *Candida* species in the overseas cases.

C. albicans, *C. glabrata* and *Candida sp.* were isolated from 15 cases, 1 case and 1 case of the 17 vitreous body culture-positive cases, respectively.

Regarding the isolation of *Candida* strains from sites other than the vitreous body, among the

domestic cases, *C. albicans*, *C. glabrata*, *C. tropicalis* and *Candida sp.* were isolated from 17 cases, 2 cases, 1 case and 1 case of the 21 blood culture-positive cases, respectively, and *C. albicans* and *C. tropicalis* were isolated from 10 cases and 2 cases of the 15 catheter culture-positive

Table 3. The sites from which the *Candida* species were isolated and the types of *Candida* isolated

Isolated region	Isolated <i>Candida</i> species	Number of cases in Japan	Number of cases in overseas
Vitreous	<i>C.albicans</i>	4	15
	<i>C.glabrata</i>	0	1
	<i>Candida</i> sp	0	1
	Negative	6	3
	Total	10	20
Anterior chamber	<i>C.albicans</i>	0	1
	Negative	1	0
	Total	1	1
Blood	<i>C.albicans</i>	17	13
	<i>C.glabrata</i>	2	2
	<i>C.tropicalis</i>	1	0
	<i>C.parapsilosis</i>	0	1
	<i>C.krusei</i>	0	1
	<i>Candida</i> .sp	1	2
	Negative	5	11
	Total	26	30

cases, respectively (including one case where both *C. albicans* and *C. parapsilosis* were isolated). The *Candida* isolated was described as non-*albicans Candida* in 1 case and *Candida* sp. in another case. Among the overseas cases, *C. albicans* and *C. krusei* were isolated from 9 cases and 1 case of the 19 blood culture-positive cases, respectively (including 1 case where both *C. albicans* and *C. parapsilosis* were isolated); the isolated *Candida* was described as *Candida* sp. in 2 cases. Furthermore, *C. albicans* was isolated from 3 of the 4 catheter culture-positive cases (including 1 case where both *C. albicans* and *C. parapsilosis* were isolated).

d) Treatment before the diagnosis of endophthalmitis (Table 1, 2:A)

The treatments administered before the diagnosis of *Candida* endophthalmitis for treating or preventing fungemia were analyzed. Of the 49 domestic cases, 14 cases (28.6%) received FLCZ therapy, 1 case (2.0%) received F-FLCZ therapy, and 10 cases (20.4%) received MCFG therapy. One case received combined 3-drug therapy, i.e., FLCZ + 5-FC + AMPH-B. Of the 49 domestic cases, 23 (46.9%) received no anti-fungal drug therapy. Of the 42 overseas cases, 10 cases (23.8%) received FLCZ therapy, 3 cases received AMPH-B therapy, and 1 case each received CPFG, VRCZ and AMPH-B + 5-FC therapy before the diagnosis.

In 2 cases, the drugs used could not be determined. Of the 42 overseas cases, 24 (57.1%) received no anti-fungal drug therapy.

e) Treatment after the diagnosis of *Candida* endophthalmitis (Table 1, 2: B)

Then, the initial treatments administered after the diagnosis of *Candida* endophthalmitis were analyzed. Among the 49 domestic cases, the initial treatment after the diagnosis was FLCZ therapy in 26 cases (53.0%), F-FLCZ in 5 cases (10.2%), MCFG in 7 cases (14.3%), AMPH-B in 2 cases, L-AMB in 1 case, MCZ in 1 case, and VRCZ in 1 case. Three cases were treated with two or more drugs in combination. Three other cases underwent curative surgical resection, without receiving any anti-fungal drug treatment after the diagnosis.

Among the 42 overseas cases, the initial treatment after the diagnosis was FLCZ therapy in 16 cases (38.1%), VRCZ therapy in 4 cases (9.5%), AMPH-B therapy in 4 cases (9.5%), CPFG therapy in 2 cases (4.7%), and L-AMB therapy in 1 case (2.4%). Seven cases (16.7%) were administered two or more anti-fungal drugs in combination. Five cases (12.0%) underwent curative surgical resection, without receiving any anti-fungal drug treatment after the diagnosis.

We additionally analyzed the treatment administered after the diagnosis of *Candida* endophthalmitis in the cases where the *Candida* species was

Table 4. Change in the treatment in relation to the type of the drug used initially

Before diagnosis	After diagnosis	Japan	Overseas
FLCZ	FLCZ	7	6
	MCFG	2	-
	AMPH-B	1	-
	MCZ	1	-
	VRCZ	-	1
	AMPH-B + 5-FC	-	1
	MCZ + 5-FC	1	-
	VRCZ + CPFG	-	2
	Vitrectomy	2	-
	Total	14	10
MCFG	FLCZ	2	-
	F-FLCZ	2	-
	MCFG	3	-
	L-AMB	1	-
	VRCZ	1	-
	MCFG + MCZ	1	-
	Total	10	-
AMPH-B	AMPH-B	-	2
	AMPH-B + 5-FC	-	1
	Total	-	3
CPFG	L-AMB	-	1
	Total	-	1
Nothing	FLCZ	17	9
	F-FLCZ	2	-
	MCFG	2	-
	AMPH-B	-	4
	VRCZ	-	3
	CPFG	-	2
	FLCZ + AMPH-B	-	1
	FLCZ + MCZ	1	-
	Vitrectomy	1	5
	Total	23	24

not identified. Among the 49 domestic cases, the causative *Candida* species remained unidentified in 12 cases. The initial treatment after the diagnosis in these 12 cases was FLCZ therapy in 9 cases (75.0%), F-FLCZ therapy in 2 cases (16.7%), and L-AMB therapy in 1 case (8.3%). Among the 42 overseas cases, the causative *Candida* species remained unidentified in 6 cases. The initial treatment after the diagnosis among these 6 cases was FLCZ therapy in 3 cases (50.0%) and VRCZ therapy in 2 cases (33.3%). In the remaining 1 case (16.7%), the treatment details remained unknown.

f) Change of treatment after the diagnosis of *Candida* endophthalmitis (Table 1, 2:A, B)

The course of treatment before and after the diagnosis of *Candida* endophthalmitis was analyzed. Twenty-six domestic cases (53.1%) had begun to receive anti-fungal therapy before the diagnosis. Among these 26 cases, 11 cases (42.3%) underwent changes or addition to the anti-fungal drug type after the diagnosis, 6 cases (23.1%) required an increase in the dose of the anti-fungal drug after the diagnosis, and in 2 cases, vitrectomy was performed immediately after the diagnosis. We then analyzed the changes in the treatment in relation to the type of drug used

Table 5. Treatment success rates reported for each treatment in Japanese cases

	Stage I	Stage II	Stage III	Stage IV	Total
FLCZ	2 of 6 (33.3%)	5 of 7 (71.4%)	5 of 26 (19.2%)	2 of 9 (22.2%)	14 of 48 (29.2%)
F-FLCZ	-	3 of 3 (100.0%)	3 of 7 (42.9%)	0 of 1 (0.0%)	6 of 11 (54.5%)
AMPH-B	-	1 of 1 (100.0%)	4 of 6 (66.7%)	0 of 3 (0.0%)	5 of 10 (50.0%)
L-AMB	-	2 of 2 (100.0%)	-	-	2 of 2 (100%)
VRCZ	-	0 of 2 (0.0%)	3 of 3 (100.0%)	0 of 2 (0.0%)	3 of 7 (42.9%)
MCFG	6 of 8 (75.0%)	0 of 3 (0.0%)	1 of 6 (16.7%)	0 of 2 (0.0%)	7 of 19 (36.8%)
5-FC	-	-	2 of 2 (100.0%)	-	2 of 2 (100.0%)
MCZ	2 of 2 (100.0%)	0 of 2 (0.0%)	2 of 3 (66.7%)	0 of 5 (0.0%)	4 of 12 (33.3%)
Vitrectomy	-	1 of 1 (100.0%)	11 of 16 (68.8%)	6 of 11 (54.5%)	18 of 28 (64.3%)

*For each stage, the total number of eyes treated with the anti-fungal drug (the number after "of") and the number of eyes treated successfully (the number before "of") are shown.

initially (Table 4). Among the 14 cases in whom endophthalmitis developed during FLCZ therapy (excluding one case included in this analysis that received multiple drug therapy), 7 cases continued to receive FLCZ therapy after the diagnosis of *Candida* endophthalmitis. In 5 of these 7 cases, increase in the dose of FLCZ was required after the diagnosis. Among the 10 cases in whom *Candida* endophthalmitis developed during MCFG therapy, MCFG was switched to FLCZ in 2 cases, and to F-FLCZ in another 2 cases after the diagnosis of *Candida* endophthalmitis. Of the 23 cases who had received no anti-fungal drug before the diagnosis, 17 cases (73.9%) were started on FLCZ therapy after the diagnosis. Among the overseas cases, 19 cases (45.2%) had begun to receive anti-fungal drug therapy before the diagnosis of *Candida* endophthalmitis. Of these 19 cases, 6 cases (26.1%) required changes/addition of the anti-fungal drug type after the diagnosis and 1 case (3.8%) required an increase of the drug dose after the diagnosis. When analyzed in relation to the drug type, 6 of the 10 cases that developed endophthalmitis during FLCZ therapy continued to receive FLCZ therapy after the diagnosis of the disease, including 1 case who needed an increase in the dose of FLCZ after the diagnosis. Of the 24 cases who had received no anti-fungal drug therapy before the diagnosis, 9 cases (37.5%) began to receive FLCZ therapy after the diagnosis, and in 5 cases (20.8%), therapeutic vitrectomy was undertaken after the diagnosis.

g) Treatment outcome by stage

A total of 66 eyes from domestic cases were

included in the analysis of the treatments administered and their outcomes in relation to the disease stage according to Pittet's classification³⁾. The treatment success rate was 62.5% for 10 eyes with stage I, 57.1% for 12 eyes with stage II, 63.3% for 31 eyes with stage III, and 24.2% for 8 eyes with stage IV disease (Table 5). The same analysis was conducted for a total of 48 eyes from the overseas cases, with the treatment success rate being 62.5% for 10 eyes with stage I, 55.6% for 19 eyes with stage II, 44.4% for 12 eyes with stage III and 26.1% for 6 eyes with stage IV disease (Table 6).

Discussion

a) Underlying diseases and risk factors

Candida endophthalmitis is a disease arising from blood-borne dissemination of *Candida*, that can be prevented by early diagnosis and treatment of candidemia. According to the domestic guidelines⁸⁴⁾ and the guidelines of the Infectious Diseases Society of America (IDSA)⁸⁵⁾, risk factors for candidemia include neutropenia, use of immunosuppressant drugs, steroids and/or anti-cancer drugs, central venous catheterization, intestinal *Candida* colonization, etc. In the present survey, cases in which the disease developed after IVH insertion were predominant in both the domestic and overseas reports, and cases in which the disease developed after surgery and cases of the disease with a history of diabetes mellitus were also frequently seen. Other than these cases, there were 6 cases of drug abuse (13.0%) among the 46 cases reported from overseas.

Table 6. Treatment success rates reported for each treatment in overseas cases

	Stage I	Stage II	Stage III	Stage IV	Total
FLCZ	4 of 7 (57.1%)	2 of 8 (25.0%)	1 of 10 (10.0%)	1 of 5 (20.0%)	8 of 30 (26.7%)
AMPH-B	1 of 2 (50.0%)	7 of 11 (64.6%)	1 of 5 (20.0%)	2 of 7 (28.6%)	11 of 25 (44.0%)
L-AMB	-	-	1 of 1 (100.0%)	-	1 of 1 (100.0%)
VRCZ	-	6 of 8 (75.0%)	2 of 2 (100.0%)	0 of 1 (0.0%)	8 of 11 (72.7%)
MCFG	-	-	-	0 of 1 (0.0%)	0 of 1 (0.0%)
5-FC	1 of 2 (50.0%)	2 of 3 (66.7%)	-	0 of 3 (0.0%)	3 of 8 (37.5%)
MCZ	-	-	-	0 of 1 (0.0%)	0 of 1 (0.0%)
CPFG	3 of 3 (100.0%)	1 of 3 (33.3%)	1 of 1 (100.0%)	-	5 of 7 (71.4%)
Vitrectomy	1 of 2 (50.0%)	1 of 1 (100.0%)	6 of 8 (75.0%)	3 of 5 (60.0%)	11 of 16 (68.8%)

*For each stage, the total number of eyes treated with the anti-fungal drug (the number after "of") and the number of eyes treated successfully (the number before "of") are shown.

b) Isolated *Candida* species

Among both domestic cases and overseas cases, *C. albicans* was the most frequently isolated *Candida* species, consistent with previous reports on cases of endophthalmitis^{86, 87)}. According to the report by Kazama et al.⁸⁸⁾, *C. albicans* was the most frequently isolated pathogen (52.1%) among 71 cases of candidemia. Thus, the tendency observed in the present study (conducted after marketing of a new anti-fungal agent) differed little from the tendency reported by Kazama et al. However, isolation of non-*albicans Candida* species as the causative pathogen has been reported increasingly frequently in recent years⁸⁷⁾. Since 2008, 5 cases of *Candida* endophthalmitis caused by non-*albicans Candida* have been reported from Japan and 3 such cases from overseas, indicating that it is necessary to select drugs for individual cases on the basis of the isolated species.

Domestic guidelines⁸⁴⁾ and the Infectious Diseases Society of America (IDSA) guidelines⁸⁵⁾ have recommended treatment methods for each type of fungus responsible for candidemia. Since the treatment recommended varies depending on the species of the fungus of the same genus *Candida*, it is essential to identify the candidal species responsible for the condition in each patient. In the present study, the percentage of cases where the candidal species had been identified was higher among the overseas cases (88.1%) than among the domestic cases (75.5%). Vitreous body/aqueous humor culture was conducted in 11 (22.4%) of the 49 domestic cases, but in 21 (45.7%) of the 46 overseas cases; thus, the pathogen causing the endophthalmitis could be

definitively identified in a higher percentage of the overseas cases. Although, vitreous body culture is often performed as a means of definite identification of the pathogen in some foreign countries, according to the report by Sallam et al.⁸⁹⁾, there was no difference in the isolation rate of *Candida* species between a needle vitreous biopsy and a vitreous biopsy using the vitreous cutter at the time of vitrectomy. It is necessary to consider the utility of culture by a needle vitreous biopsy in the future.

c) Treatment before the diagnosis of *Candida* endophthalmitis

Candida endophthalmitis is a complication of fungemia and can be prevented by appropriate anti-fungal drug therapy for fungemia. In addition, the length of time from the onset of fungemia to the first visit to an ophthalmology clinic is also important. In the present study, few reports provided information about the period from fungemia onset to the first ophthalmology clinic visit. Meanwhile, in the present study, 53.1% of the domestic cases and 42.9% of the overseas cases were diagnosed as having *Candida* endophthalmitis, although they had already received anti-fungal drug therapy before the diagnosis. This finding indicates that fungemia is complicated by endophthalmitis in many cases and that it is important to promote proper use of anti-fungal drugs when dealing with fungemia.

d) Treatment after the diagnosis of *Candida* endophthalmitis

After the diagnosis of *Candida* endophthalmitis, FLCZ was the most frequently selected drug for

the treatment according to both domestic and overseas reports. The second most frequently selected drug was MCFG for domestic cases and VRCZ for overseas cases. When dealing with cases not responding to FLCZ therapy, domestic guidelines⁸⁴⁾ recommend considering a switch from FLCZ to VRCZ, MCFG, ITCZ, AMPH-B, L-AMB or MCZ, or administering FLCZ in combination with MCFG, L-AMB, AMPH-B or 5-FC, thus providing numerous alternatives for treatment, whereas the American (IDSA) guidelines⁸⁵⁾ recommend the use of VRCZ or L-AMB for FLCZ-resistant cases. This probably explains why VRCZ was used often in overseas cases. Therapeutic vitrectomy was carried out after the diagnosis of endophthalmitis in 16 domestic cases and 13 overseas cases. Although the domestic guidelines do not clearly define the timing for vitrectomy, this operation was performed in the earlier stages in foreign countries than in Japan. This probably reflects the tendency to perform vitrectomy with the additional purpose of definitively identifying the pathogen. According to domestic reports, anti-fungal drug treatment after vitrectomy was ongoing in 8 of the 16 cases, while no information was available about the status of such drug therapy in the remaining 8 cases. Also, little information was available in the reports about the route by which the anti-fungal drug was administered, leaving it unclear whether the drugs were administered by injection into the vitreous body or by intravenous injection.

e) Changes in treatment after the diagnosis of *Candida* endophthalmitis

Among the domestic cases that had begun to receive anti-fungal drug treatment before the diagnosis of *Candida* endophthalmitis, the most commonly employed treatment alternative after the diagnosis was change/addition of antifungal drugs (42.3%). The percentage of such cases from overseas reports was 29.9%. These results suggest the importance of promotion of proper use of anti-fungal agents for fungemia in Japan.

In regard to the treatment after the diagnosis of *Candida* endophthalmitis, among the cases that had received no anti-fungal drugs before the diagnosis, FLCZ therapy was started after the diagnosis in 73.9% of all domestic cases, indicating that FLCZ is used as the drug of first choice for *Candida* endophthalmitis in Japan. Among the overseas cases, FLCZ treatment was started

after the diagnosis in 37.5% of the cases who had received no anti-fungal drugs before the diagnosis of endophthalmitis. This result indicates that while FLCZ is often selected for the treatment of endophthalmitis in foreign countries, other methods are also used in many overseas cases, indicating that FLCZ is not the only drug used as the first-line drug for endophthalmitis in foreign countries. IDSA guidelines also recommend the vitrectomy for severe cases, indicating that FLCZ is not the only drug used as the first-line drug for endophthalmitis in foreign countries.

f) Treatment outcome by stage

The data given in Table 5 and 6 confirm that FLCZ therapy and vitrectomy are often applied for the treatment of *Candida* endophthalmitis in Japan, and that FLCZ, AMPH-B and VRCZ therapy, as also vitrectomy, are often used for the treatment overseas. It was thus shown that FLCZ is most often selected as the drug for treatment after the diagnosis of *Candida* endophthalmitis. The overall treatment success rate with FLCZ was not high (29.2% in domestic cases and 26.7% in overseas cases). The present study was based on case reports published in journals and may have been biased in that treatment may have been difficult in many of the reported cases covered by this study and that there was a relatively high number of cases that failed to respond to FLCZ, the drug most often used for the treatment of *Candida* endophthalmitis. The difference in the treatment success rate between the present study (29.2%) and the report by Kazama et al. (50.0%)⁸⁸⁾ probably reflects such biases. It seems therefore probable that the treatment success rate with FLCZ was underestimated in the present study. Although vitrectomy was not frequently selected as the first-line therapy for domestic cases in the present study, the frequency of vitrectomy was not low; it was applied for 28 cases (42.4%) among the 66 eyes. This indicates that vitrectomy tends to be selected in Japan for cases that fail to respond to other treatment methods. The data from domestic cases additionally suggest that FLCZ is effective for stage II cases, and that vitrectomy is effective for stage III and IV cases. The data from overseas cases suggest that AMPH-B or VRCZ is effective for stage I and II cases, and vitrectomy is effective for stage III and IV cases.

A bibliographic investigation was carried out on the treatment of endogenous *Candida* endophthalmitis in domestic cases and overseas cases reported during the period from 2000 to 2011, with an analysis conducted of the underlying diseases, risk factors, the isolated species, treatment methods and treatment outcomes by the disease stage. A retrospective investigation of the treatment of this disease in future may provide further information useful for the treatment of endogenous *Candida* endophthalmitis.

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