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【 CASE REPORT 】

Clinical Characteristics of Patients with Cryptococcal Meningitis in Hokkaido: A Case Series

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Abstract:

We retrospectively reviewed the medical histories, examination results, treatments, and prognoses of nine patients with cryptococcal meningitis who were diagnosed and treated at Hokkaido University Hospital and its affiliated hospitals over the past 10 years. Cryptococcal meningitis can develop even in immunocompetent hosts, and its prognosis is poor owing to diagnostic difficulties and delayed treatment. Although liposomal amphotericin B and oral 5-fluorocytosine are standard therapies, voriconazole or intraventricular administration of amphotericin B may also be considered treatment options for refractory patients. Some patients develop delayed exacerbations owing to immunological mechanisms that require steroid therapy.

Key words: cryptococcus, cryptococcal meningitis, case series, HIV-negative, Hokkaido, Japan

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Introduction

Cryptococcal meningitis is a general term for meningitis or central nervous system (CNS) disease caused by the fungus *Cryptococcus*. The disease often develops in immunocompromised patients, such as those with acquired immunodeficiency syndrome (AIDS), malignant lymphoma, or previous immunosuppressive drug use; however, it can also develop in healthy individuals without any underlying diseases.

Cryptococcal meningitis is the most frequent invasive fungal infection among healthy individuals in Japan (1). Nineteen species of *Cryptococcus* have been identified, including two that can cause infections in humans: *C. neoformans* (serotypes A and D) and *C. gattii* (serotypes B and C) (2). In Japan, *C. neoformans* type A is the causative organism in most cases of pulmonary infections and meningitis (3). *C. gattii* outbreaks have been reported in immunocompromised individuals, particularly in Australia and North America; however, some cases have recently been reported in Japan (4, 5). *C. neoformans* is associated with soil contaminated with pigeon droppings, suggesting the involvement of the soil as a source of infection. The inhalation of floating fungi results in the formation of the first infection foci in the lungs, which have a high affinity for the CNS. Furthermore, *C. neoformans* can enter the bloodstream and cause hematogenous cerebral meningitis.

Hokkaido is located in the northernmost prefecture of Japan and has a cool and humid climate, with approximately 70% of its land being covered by forests. It is a typical rural area of Japan, with a relatively low population density and many residents engaging in primary industries. Several cases of *Cryptococcus* spp. infection are reported annually in this region (6). However, there have been no reports of multicenter evaluations of cryptococcal meningitis in Hokkaido, and patient characteristics, treatment trends, and prognostic factors remain unclear.

In this study, we retrospectively reviewed patients diagnosed with cryptococcal meningitis or cerebral cryptococco-

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Table 1. Background Data for Nine Patients.

Patient No.	*Age*	*Sex*	*Symptoms of onset*	*Medical history*	*HIV*	*Occupation*	*Immunosuppressant, or other medication (/day)*	*Activities of daily living*	*Travel history*	*Suspected exposure*
1	34	F	Drowsy	Cervical cancer hepatitis B pulmonary embolism	(-)	N/A	Warfarin, lipidol, magnesium oxide	Independent	Korea China Canada	N/A
2	81	M	General malaise anorexia	Rheumatoid arthritis interstitial pneumonia obsolete tuberculosis	(-)	N/A	PSL 7 mg, tacrolimus 3 mg	Independent	N/A	N/A
3	60	M	Dysarthria general malaise, discomfort in the right upper extremity	Chronic neutrophilic leukemia	(-)	Bus driver	Hydroxycarbamide 500 mg	Independent	N/A	N/A
4	41	F	Headache nausea neck pain	Rheumatoid arthritis	(-)	N/A	Tacrolimus 3 mg salazosulfapyridine 1,000 mg methotrexate 16 mg/week PSL 20 mg tocilizumab (dose was unknown)	Independent	N/A	N/A
5	75	F	General malaise fever posterior neck pain	Hepatitis B hypertension obsolete tuberculosis	(-)	N/A	(-)	Independent	N/A	N/A
6	67	F	Fever headache loss of Consciousness	Polymyalgia rheumatica	(-)	N/A	PSL 20 mg	Independent	N/A	N/A
7	78	F	None	Lung cancer rheumatoid arthritis	(-)	N/A	PSL 8 mg, gefitinib	Independent	(-)	Balcony
8	78	M	Unsteadiness, falling	Numbness (unknown cause)	(-)	Farmer	PSL 5 mg	Independent	N/A	Well water
9	74	M	Unsteadiness, falling	Thalamic hemorrhage	(-)	Farmer	(-)	Independent	(-)	N/A

ADL: activities of daily living, M: male, F: female, N/A: not available, PSL: prednisolone

sis at a neurology department in Hokkaido over the past 10 years.

Case Reports

We retrospectively evaluated the clinical course of cryptococcal meningitis in patients whose data were available, who had been diagnosed between January 1, 2010, and August 31, 2022, and who had received treatment at the Department of Neurology of Hokkaido University Hospital and its affiliated hospitals. We recruited nine patients treated at Obihiro Kosei General Hospital, Hokkaido University Hospital, Japanese Red Cross Asahikawa Hospital, and the National Hospital Organization Hokkaido Medical Center. The following data were obtained: patient age, sex, medical history, medication history, and cerebrospinal fluid (CSF) and blood test results, including culture tests, imaging findings, treatment details, infection or treatment-related complications, and outcomes. In addition, in the present study, the worsening of symptoms and laboratory findings during cryptococcal meningitis treatment was described as follows: poor response, no improvement in neurological symptoms or CSF findings even after the acute phase treatment; relapse, patients with CSF findings and neurological symptom who achieved improvement once but showed increased spinal fluid cell counts, re-positive CSF cultures, and neurological symptom exacerbation after conversion to maintenance therapy; delayed exacerbation, patients whose CSF findings and neurological symptoms were re-exacerbated by immunological mechanisms and improved with corticosteroid therapy.

For statistical evaluations, *t*-tests and chi-square tests were used. Statistical significance was defined as $p<0.05$. This study was approved by the Institutional Review Boards of Obihiro Kosei General Hospital and other hospitals, and informed consent was obtained from the institution's website through an opt-out form.

Results

1. Background characteristics (Table 1)

The participants included 4 men and 5 women (mean age ±standard deviation, 65.3±16.1 years old; range, 41-81 years old). Symptoms experienced at the onset were general malaise in three patients, neck pain or headache in three patients, unsteadiness in two patients, and a fever in two pa-

Table 2. Summary of Blood and Spinal Fluid Analysis.

Patient No.	*Initial pressure (mmH_2O)*	*Cell count ($/mm^3$)*	*Mononuclear cells ($/mm^3$)*	*Polymorphonuclear cells ($/mm^3$)*	*Protein (mg/dL)*	*Glucose (mg/dL)*	*Blood glucose (mg/dL)*	*IgG index*
1	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
2	110	150	129	21	370	58	223	1.55
3	N/A	500	464	36	86	19	102	1.17
4	>340	141	65	76	77	8	288	7.26
5	>340	56	44	12	49	28	153	1.35
6	>340	378.7	83.7	274.7	152.9	17	163	2.03
7	N/A	1	1	0	38	65	124	0.35
8	>350	13	9.7	3.7	80.7	43	134	0.84
9	300	30	27	3	92	2	200	0.93

N/A: not available

tients. Patient 7 was asymptomatic. The patients had different comorbidities in their medical histories; in particular, one patient had leukemia, a hematological disease; three patients had rheumatoid arthritis; one patient had polymyalgia rheumatica, a collagen and autoimmune disease; one patient had lung cancer; two patients had tuberculosis; and two patients had hepatitis B. All patients tested negative for human immunodeficiency virus (HIV) infection.

Five patients continued immunosuppressive treatment, including prednisolone (PSL), for collagen diseases and numbness (unknown cause). Patient 4 was treated with tacrolimus (3 mg/day), salazosulfapyridine (1,000 mg/day), tocilizumab (dose unknown), and methotrexate 16 mg/week, in addition to PSL 20 mg/day. The other three patients had no history of immunodeficiency and were not receiving any medications. One patient had a history of recent overseas travel to Asia and Canada, whereas the other eight had no or an unknown travel history. The source of exposure to *Cryptococcus* was unknown in seven patients.

2. CSF findings (Table 2)

A CSF analysis was performed in all patients before treatment, except for Patient 1, who had cerebral edema. A high CSF opening pressure was noted in 6 patients, including a CSF opening pressure >300 mmH_2O in 5 patients. In patients 4 and 5, it increased to approximately 1,000 mmH_2O during the course of the disease. The mean CSF cell count was 158.71±172.66/mm^3, with most cells being mononuclear. The CSF protein levels were elevated in most patients (118.20±100.41 mg/dL), glucose levels were reduced in 6 patients (30.00±21.62 mg/dL), and the IgG index was high in 7 patients (1.94±2.07) and tended to decrease during treatment.

3. Antigen and culture findings (Table 3)

Blood cryptococcal antigen was positive in all nine patients, and cryptococcal antigen titers in the CSF were analyzed in six patients using latex agglutination before treatment. Four patients had more than 1:512 measurements (higher than the measurement limit), and 1 patient had 1:256 measurements on semi-quantification. One patient tested positive in a qualitative test. *C. neoformans* was detected by blood culture in three patients and CSF culture in five patients. However, because the laboratories in these clinics could not distinguish between *C. neoformans* and *C. gattii*, we submitted CSF and lung tissue samples from patients 1, 3, and 9 to the National Institute of Infectious Diseases for Genetic Screening, which confirmed the diagnosis of *C. gattii* in patient 1 and *C. neoformans* in patients 3 and 9.

4. Imaging findings (Table 3)

Brain magnetic resonance imaging revealed gadolinium-enhanced T1-weighted hyperintense lesions along the pia mater in three patients, nodular lesions or cryptococcoma in four patients, soap bubble appearance in one patient, and hydrocephalus in two patients. One patient showed ventricular enlargement consistent with age-related changes, and two patients showed no abnormal imaging findings. Patient 7 lacked CSF findings of meningitis, and there was a need to differentiate from brain metastases secondary to lung cancer; however, a brain biopsy was not performed because of the patient's general condition. Furthermore, since typical ring enhancement was not found, and the nodular lesion presented a soap bubble pattern, we concluded that it was *Cryptococcus* meningitis. Chest computed tomography (CT) revealed lung lesions in patients 1, 2, 7, and 9. A lung biopsy was performed in two patients, and pulmonary cryptococcosis was diagnosed histopathologically.

5. Treatment (Table 4A)

The mean period from the symptom onset to treatment initiation was 4.89±2.28 weeks (range, 1-9 weeks). All patients were treated with intravenous liposomal amphotericin B (L-AMB) and oral 5-fluorocytosine (5-FC). The duration of acute-phase treatment was 8.56±8.85 weeks (range, 3-33 weeks). Voriconazole (VRCZ) was administered to patient 5 during the acute-phase treatment. Prior to the diagnosis of meningitis, antibiotics such as meropenem, ceftriaxone, and anti-tuberculosis drugs were administered as empirical therapies for meningitis in patients 3, 4, and 5. Patient 9 had hydrocephalus; therefore, bilateral ventricular drainage was performed. After confirming negative CSF cultures and administering intravenous L-AMB for four weeks, all patients were switched to intravenous or oral fluconazole (FLCZ).

Patient 4 had a poor response to treatment, whereas five patients (Patients 1, 3, 7, 8, and 9) were diagnosed with re-

Table 3. Antigen, Culture, and Imaging Findings.

Patient No.	*Antigen*		*Culture*		*Bacterial species*		*Brain lesion on MRI*	*Airway or lung lesion*
	CSF (titer)	Blood	CSF	Blood	Each hospital	NIID		
1	1:8*	(+)	(-)	(+)	*C. neoformans*	*C. gattii***	Cyptococcoma	(+)
2	1:512	1:512	(-)	(-)	(-)	N/A	Ventriculomegaly	(+)
3	1:256	(+)	(+)	(-)	*C. neoformans*	*C. neoformans*	Gd enhanced nodular lesions in parietal lobe, brain stem, cerebellum	(-)
4	>1:512	(+)	(+)	(+)	*C. neoformans*	N/A	Gd hyperintensity lesions along the pia mater stroke	(-)
5	>1:512	(+)	(+)	(-)	*C. neoformans*	N/A	(-)	(-)
6	N/A	(+)	(-)	(-)	(-)	N/A	(-)	(-)
7	(-)	(+)	(-)	(-)	*C. neoformans***	N/A	Cryptococcoma Gd enhanced lesions along the pia mater soap bubble appearance	(+)
8	(+)	(+)	(+)	(-)	*C. neoformans*	N/A	Gd enhanced lesions along the pia mater and nodular lesions in left basal ganglia FLAIR hyperintensity lesions in cerebral white matter hydrocephalus	(-)
9	>1:512	(+)	(+)	(+)	*C. neoformans*	*C. neoformans*	Hydrocephalus	(+)

* After treatment.

**Lung tissue sample.

CSF: cerebrospinal fluid, NIID: National Institute of Infectious Diseases, MRI: magnetic resonance imaging, N/A: not available, Gd: gadolinium, FLAIR: fluid-attenuated inversion recovery, *C. neoformans*: *Cryptococcus neoformans*, *C. gattii*: *Cryptococcus gattii*

lapse of cryptococcal meningitis after switching to FLCZ. L-AMB was restarted in patients 3, 7, 8, and 9, and VRCZ was administered in patients 1, 3, and 9. Patients 7 and 9 showed improvement, but the other 4 (Patients 1, 3, 4, and 8) were considered to have a poor response to treatment and received intraventricular administration of amphotericin B (AMPH-B). It was started at a low dose and gradually increased to 0.5-1.0 mg and was effective in all patients. Ommaya reservoirs were placed on patients 1, 3, and 4. Three patients received steroids after delayed exacerbation. Patient 9 had persistently high antigen titers, making it difficult to determine the precise efficacy of L-AMB and distinguish between relapse and delayed exacerbation. As the patient responded to steroids, he was diagnosed with delayed exacerbation other than relapse of cryptococcal meningitis. In addition, patient 9 tested positive for anti-N-methyl-D-aspartate receptor (NMDAR) and anti-titin antibodies in the CSF.

6. Response to treatment and the prognosis (Table 4B)

In 5 patients with a positive CSF culture, the period for negative conversion was 13.80±3.54 days, and the period for obtaining negative findings with India ink staining was 46.25±35.15 days. However, Patient 5 remained positive for India ink staining until they were transferred to a different hospital (for 92 days). CSF antigen titers were measured after treatment in 6 patients, with negative or one-time results in 3 patients, 1:128 in 1 patient, and ≥1:512 in 2 patients on semi-quantification. The treatment ranged from 3.5 months to 3.5 years. The modified Rankin Scale (mRS) score ranged from 1 to 6, and 8 of 9 patients had a score of ≥3.

Two patients died, and seven recovered, but only one improved to a presymptomatic condition. Patients with a poor prognosis in this study, especially those with an mRS score ≥5, had significantly lower CSF cell counts at the onset than those with an mRS score <5 (48.2/mm^3 vs. 342.9/mm^3, p= 0.01). Although no significant differences were found, these patients tended to be relatively old, use immunosuppressive drugs, and have elevated intracranial pressure, persistently positive CSF India ink stains, and high CSF antigen titers after acute-phase treatment (>1:128) (Table 5).

Discussion

We retrospectively reviewed nine patients diagnosed with cryptococcal meningitis in Hokkaido, Japan. There are already a few single-center case series of cryptococcal meningitis cases in Japan (7-9); However, this is the first report of a multicenter evaluation in a given prefecture.

In epidemiological evaluations comparing the results of this study with those of a national survey of disseminated cryptococcal infections from 2014 to 2015 (10) (n=123), the proportion of healthy individuals was slightly higher (33% vs. 15%) and the number of HIV-positive patients lower (0% vs. 6.5%). Slightly fewer patients presented with a fever (22% vs. 60%) and disorders of consciousness (22% vs. 43%), whereas the proportion of patients with headache/neck pain was similar between the present and previous studies (33% vs. 30%). The positive rates of the CSF or blood culture were lower (67% vs. 88%), while those of the CSF or blood cryptococcal antigen titer were higher (100% vs. 51%) than those in the national survey, although these differences were not statistically significant. CSF findings, imaging findings, and other prognostic factors in the present

Table 4A. Treatment Details.

Patient No.	*Duration to start treatment (weeks)*	*Treatment of antifungal drug and dose (/day)*	*Acute phase treatment period (weeks)*	*Relapse*	*Additional treatment after relapse (/day)*	*Intrathecal injection*
1	4	① L-AMB 6 mg/kg 5-FC 100 mg/kg ② FLCZ/VRCZ/ITCZ (each dose was unknown)	8	(+)	Restart intrathecal injection ITCZ → VRCZ (dose is unknown)	AMPH-B 0.5 mg (increasing from 0.05 mg)
2	6	① FLCZ 400 mg (10 mg/kg) ② L-AMB 100-180 mg (2.5-4.5 mg/kg) 5-FC 4,000 mg (100 mg/kg) ③ FLCZ 100-400 mg	33	(-)	(-)	(-)
3	1	① L-AMB 250 mg (4.38 mg/kg), 5-FC 3,000 mg (≒50 mg/kg) ② FLCZ 200 mg	4	(+)	L-AMB 325 mg (5.8 mg/kg) VRCZ 800 mg	AMPH-B 0.5 mg (increasing from 0.05 mg)
4	8	① L-AMB 350 mg (6 mg/kg) 5-FC 8,000 mg (137 mg/kg) ② FLCZ 800 mg	6	(-)	(-)	AMPH-B 0.45 mg (increasing from 0.05 mg)
5	4	① L-AMB 200 mg (5 mg/kg) 5-FC 6,000 mg (150 mg/kg) VRCZ 300 mg ② FLCZ 200-400 mg	6	(-)	(-)	(-)
6	4	① L-AMB 150 mg (3.3 mg/kg) 5-FC 5,000 mg (110 mg/kg) ② FLCZ 400 mg	3	(-)	(-)	(-)
7	4	① L-AMB 100 mg (2.5 mg/kg) 5-FC 4,000 mg (100 mg/kg) ② FLCZ 200 mg	4	(+)	L-AMB 100 mg (2.5 mg/kg)	(-)
8	4	① L-AMB 150 mg (3.4 mg/kg) 5-FC 4,000 mg (≒100 mg/kg) ② FLCZ 400 mg	9	(+)	L-AMB 150-300 mg 5-FC 4,000 mg (≒ 100 mg/kg) → FLCZ 800 mg 5-FC 4,000 mg (≒ 100 mg/kg)	AMPH-B 1.0 mg (increasing from 0.25 mg)
9	9	① L-AMB 250 mg (6 mg/kg) 5-FC 2,000 mg (50 mg/kg) ② FLCZ 200 mg	4	(+)	L-AMB 200-250 mg → VRCZ 200 mg	(-)

L-AMB: liposomal amphotericin B, 5-FC: 5-Fluorocytosine, FLCZ: fluconazole, VRCZ: voriconazole, ITCZ: itraconazole, AMPH-B: amphotericin B

Table 4B. Treatment Response and Prognosis.

Patient No.	*Period of negative conversion (days)*		*Final titer of antigen in CSF (Period from initiation of treatment)*	*Delayed exacerbation*	*Additional steroid treatment*	*Encephalitis-related antibody*	*Treatment duration*	*mRS*
	CSF culture	India ink staining						
1	(-)	(-)	1:1 (11 months)	(+)	mPSL pulse tapered from PSL 60 mg	N/A	Over 2.5 years	1
2	(-)	(-)	Negative (2 years and 3 months)	(-)	(-)	N/A	About 3.5 years	4
3	14	N/A	1:1 (8 months)	(+)	mPSL tapered from PSL 40 mg	N/A	About 9 months	3
4	16	58	>1:512	(-)	(-)	N/A	About 3.5 months	6
5	9	Not converted to negative for 92 days	>1:512 (3 months)	(-)	(-)	N/A	About 9-15 months	5
6	(-)	16	N/A	(-)	(-)	N/A	N/A	4
7	(-)	(-)	N/A	(-)	(-)	N/A	About 5 months	6
8	19	96	N/A	(-)	(-)	N/A	About 1 year	5
9	11	15	1:128 (8 months)	(+)	mPSL pulse taper from PSL 40 mg	anti-NMDAR antibody	Over 1 year	5

CSF: cerebrospinal fluid, N/A: not available, PSL: prednisolone, mPSL: methylprednisolone, NMDAR: N-methyl-d-aspartate receptor, mRS: modified Rankin Scale

Table 5. Statistical Analysis.

		mRS ≥ 5	*mRS <5*	p value
n		5	4	
Age (years)		69.2±17.1	60.5±14.2	0.485
Use of immunosuppressant (n)		3	2	0.841
Opening pressure >300 mmH_2O (n)		4	1	0.527
CSF white cell count (/μL)		48.2±49.9	342.9±145.1	0.011
Duration to start treatment (weeks)		5.8±2.23	3.75±1.79	0.229
Positive CSF culture (n)		4	1	0.271
Acute phase treatment period (weeks)		5.8±1.83	12±12.27	0.358
Period of negative conversion (days)	*CSF culture*	11.0±6.54	3.5±6.06	0.163
	India ick staining	52.2±31.10	5.33±7.54	0.126
Relapse (n)		3	2	0.841
Final cryptococcal antigen titer in CSF >1:128 (n)		3	0	0.083

CSF: cerebrospinal fluid, mRS: modified Rankin Scale

study were similar to those previously reported (11, 12).

Focusing on the bacterial species, our study included one case of *C. gattii* with a favorable outcome. However, *C. gattii* is generally associated with poorer responses to treatment and a worse prognosis than *C. neoformans* (13, 14). The fact that the patient was immunocompetent, had only one poor prognostic factor [altered consciousness (15)] and also underwent intraventricular administration may have led to an improved prognosis. According to Japanese guidelines and reviews, L-AMB+5-FC is the first choice of acute treatment, and FLCZ is used as a maintenance therapy. In the present study, all patients were started on L-AMB+5-FC and confirmed to be CSF culture-negative. However, some relapses were noted. The timing of relapse was often after switching to FLCZ, and in some cases, the CSF findings improved after resuming L-AMB or increasing the dose of FLCZ, suggesting that the short duration of L-AMB treatment (usually four weeks) and low dose of FLCZ were the causes of relapse.

In some cases, the use of VRCZ as an alternative to FLCZ has resulted in disease control, although evidence of its therapeutic effect in cryptococcal meningitis is lacking. VRCZ was used in four patients in this study; two of them were treated with VRCZ in combination with acute therapy, and two received it as additional therapy after relapse. VRCZ for cryptococcal meningitis has been reported to be effective in patients with a poor response to FLCZ (16), but a further investigation of its efficacy is needed. In particular, VRCZ should be considered in patients who are unable to continue intravenous L-AMB therapy because of renal dysfunction or other side effects.

Intraventricular AMPH-B should also be considered for patients who are deemed to have an inadequate response to other antifungal agents or for whom it is difficult to continue intravenous administration owing to adverse effects, such as renal dysfunction or hypokalemia. If treatment is confirmed to be effective, placement of an Ommaya reservoir can facilitate intraventricular administration of antifungal agents on an outpatient basis. In the present study, intraventricular administration was performed in four patients, including those with a poor response and relapsed cases. Their prognoses were expected to improve with intraventricular therapy because they were relatively young and had lived independently prior to admission. Among those four patients, two improved, one had an mRS score ≥5, and one who had been treated with multiple immunosuppressants died of sepsis and cardiopulmonary arrest after Ommaya reservoir implantation. While intraventricular administration of AMPH-B is well tolerated in young HIV-positive patients (17), the adverse effects and risk of surgical complications may interfere with the good outcomes among patients taking multiple immunosuppressant drugs, those who are relatively old, those who have a low performance status, or those with a tendency to experience a decline in activities of daily living due to long-term treatment.

In three patients, delayed exacerbation was suspected during treatment with antifungal agents, and additional steroid therapy improved the symptoms and CSF findings. Furthermore, delayed exacerbations of cryptococcal meningitis owing to immunological mechanisms have been reported. The proposed mechanism involves inhibition of immune suppression by antifungal agents through the effects of glucuronoxylomannan, resulting in CSF vascular endothelial growth factor expression, increased vascular permeability and intracranial pressure, and blood-brain barrier (BBB) disruption (3). In contrast, in patient 9, who showed delayed exacerbation, anti-NMDAR antibodies were detected before antifungal treatment. The coexistence of cryptococcal meningitis and anti-NMDAR antibody encephalitis has been reported previously (18-20); however, the pathogenesis of autoimmune encephalitis remains unclear. Taken together, these reports suggest that autoantibodies may be one mechanism underlying the delayed exacerbation of cryptococcal meningitis.

The usefulness of steroid therapy for delayed exacerbations has been studied in both HIV-positive and HIV-negative patients. No marked difference in mortality or adverse effects was noted between the dexamethasone and

control groups in a randomized trial of HIV-positive patients with cryptococcal meningitis (21). In contrast, a cohort study of HIV-negative patients reported better prognoses in those who received high-dose steroids than in those who did not (22). In the present study, three patients who received steroids for delayed exacerbations were not immunosuppressed, and two of them showed an improved mRS; no patients died. Among immunocompetent patients, delayed exacerbations are expected to improve with treatment. Initiation of steroid therapy should be considered when a patient's condition worsens during meningitis treatment, in addition to adjusting the antifungal agent dosage.

Several limitations associated with the present study warrant mention. First, the small number of cases limited the statistical analysis. Second, the retrospective design of the study limited the assessment of some features, as information could not be obtained from the medical records or examined. Third, genetic screening to identify *C. neoformans* or *C. gattii* was not performed in some cases, and the prognosis could not be evaluated based on the species.

Conclusions

We herein report the clinical course, laboratory findings, treatment, and prognosis of nine patients with cryptococcal meningitis and cerebral cryptococcosis diagnosed in Hokkaido, the northernmost prefecture of Japan. Similar to previous reports, cryptococcal meningitis cases in the present study were refractory to treatment and had a poor prognosis. If the symptoms do not improve with standard treatment, VRCZ or intraventricular AMPH-B may be a treatment option. If antifungal agents are ineffective, delayed exacerbation caused by immunological mechanisms should be suspected and steroid therapy considered.

The authors state that they have no Conflict of Interest (COI).

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