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Case report

Fingolimod-associated cryptococcal meningitis in a patient with Multiple Sclerosis: A case report and literature review

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ABSTRACT

A 65-year-old woman with Multiple Sclerosis treated with fingolimod developed headaches and convulsions. Cerebrospinal fluid (CSF) culture indicated *Cryptococcus neoformans*. A literature review of 20 cases of cryptococcal meningitis indicated that headache was the most common initial symptom, and all cases were positive for serum and/or CSF cryptococcal antigens.

Introduction

Cryptococcus neoformans can cause potentially lethal disseminated infections including meningitis in both persons living with acquired immunodeficiency syndrome and in other immunosuppressed populations. The latest immunosuppressive therapies used to treat a wide range of autoimmune and inflammatory diseases may increase the risk of cryptococcal infections. We describe a woman with Multiple Sclerosis (MS) who developed cryptococcal meningitis. The patient was being treated with fingolimod, which inhibits lymphocyte migration from the lymph nodes and reduces peripheral blood lymphocyte count, a risk factor for cryptococcal infection.

Case presentation

We describe the case of a 65-year-old woman who experienced a 2-week course of gradually worsened unilateral headaches and anorexia. She presented to our hospital with an episode of loss of consciousness and newly onset convulsive seizure. Thirteen years prior, she presented with primary complaints of headaches and gait disturbances. She was diagnosed with relapsing/remitting MS based on brain magnetic resonance imaging (MRI), which initially revealed periventricular and juxtacortical T2 hyperintense lesions (Fig. 1), followed by new right cerebral peduncle and left middle cerebellar peduncle lesions (3 months later). Oligoclonal bands were absent from the cerebrospinal fluid (CSF).

Twelve years ago, she started taking fingolimod as a disease-modifying treatment (DMT) for MS. Among the limited treatment options available at the time (i.e. interferon β-1a/1b and fingolimod), fingolimod was chosen over interferon β because a) she had a history of depression, for which interferon β is contraindicated due to possible exacerbation of depressive symptoms, and b) several factors including brain stem lesions and short interval between relapses suggested an active disease calling for higher efficacy therapy.

After the introduction of fingolimod, the patient has been clinically stable with mild disability at the Kurtzke Expanded Disability Status Scale (EDSS) score 1, without evidence of recurrence or progressive atrophy on brain MRI. Peripheral blood lymphocyte count remained at 400–600/μL, slightly below the reference range, a common side effect of fingolimod, but never below 200/μL, a criterion for discontinuing the drug. Because she was clinically stable, fingolimod was continued for 12 years without switching to other DMTs.

On examination upon this admission, she was afebrile. Laboratory tests revealed mild peripheral lymphopenia (520/uL). Head CT and brain MRI with and without gadolinium contrast enhancement showed no new lesions nor meningeal enhancement (Fig. 2). Seizure was refractory to levetiracetam and fosphenytoin. Progressive headache and refractory seizure suggested a possible central nervous system infection. A CSF examination performed two days after hospitalization revealed an opening pressure of 14 cm H_2O, a cell count of 15/μL (80 % mononuclear cells), 52 mg/dL protein, and 62 mg/dL glucose (174 mg/dL blood glucose).

The CSF was positive for cryptococcal antigen (1:1024). Multiplex

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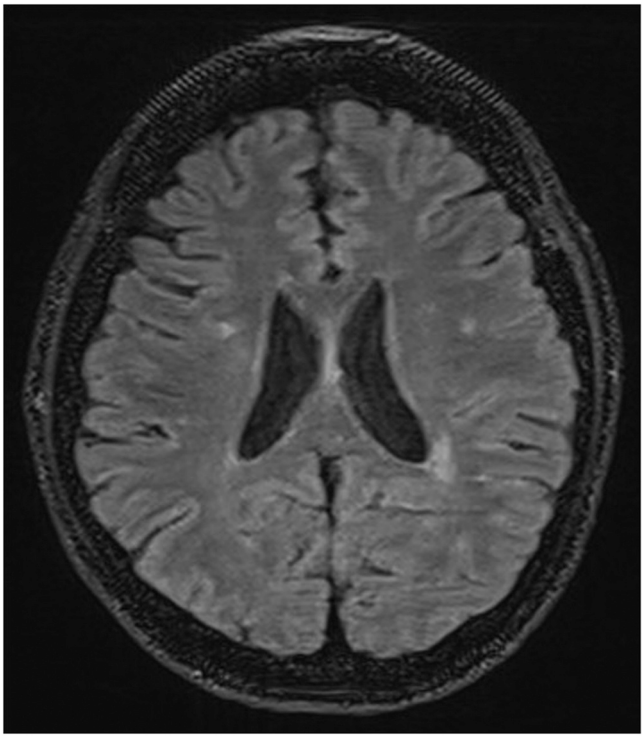

Fig. 1. Brain MRI at the time of MS diagnosis (13 years ago), which revealed periventricular and juxtacortical T2 hyperintense lesions.

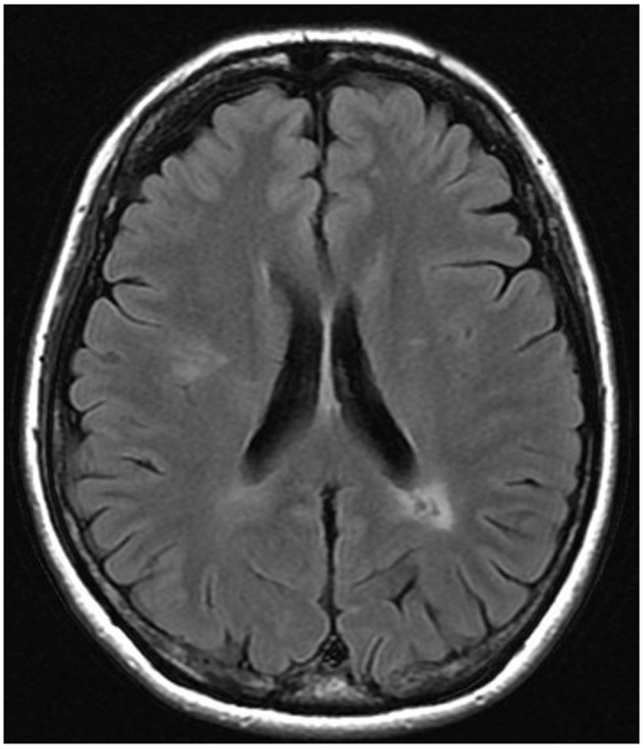

Fig. 2. Brain MRI on this admission, with no new lesions.

polymerase chain reaction (BioFire® FilmArray® Meningitis/Encephalitis Panel) was positive for *Cryptococcus*; it was finally identified as *C. neoformans* using CSF culture. CSF myelin basic protein levels were marginally elevated at 111.5 pg/mL (reference: < 102 pg/mL); however, the IgG index remained within normal limits at 0.672 (reference: < 0.73). Adenosine deaminase (ADA) levels were within the normal range at 4.2 IU/L, and both *Treponema pallidum* antibody and oligoclonal bands were negative. Blood was also positive for cryptococcal antigen (1:1024); however, blood cultures were negative. Cryptococcal meningitis was diagnosed. Induction therapy with liposomal amphotericin B (5 mg/kg intravenously once daily) and flucytosine (25 mg/kg orally, four times a day) was started on hospital day 2. Her headaches subsided within a few days.

On hospital day 5, antiseizure medications were switched from intravenous to oral drugs, comprising levetiracetam, lacosamide and clobazam, and no recurrence of seizure was observed.

Four days after treatment initiation, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations increased to 158 U/L (reference range, 8–38) and 364 U/L (reference range, 4–44), respectively, and drug-induced liver injury was suspected. Considering the importance of treating cryptococcal meningitis, liposomal amphotericin B was continued as a key drug. Flucytosine and the antiepileptic drug, clobazam, which was more likely to cause liver dysfunction than levetiracetam and lacosamide (which were administered simultaneously), were discontinued. The AST and ALT concentrations gradually improved to 25 U/L and 42 U/L, respectively, over the 2 weeks after drug discontinuation. A follow-up CSF examination was performed 1 week and 2 weeks after treatment. *C. neoformans* was still positive in the first follow-up CSF culture; however, the CSF culture was negative 2 weeks after treatment. In general, fluconazole is proposed to add to liposomal amphotericin B as the induction treatment for cryptococcal meningitis in the absence of flucytosine. However, concerns arose regarding the addition of a new drug in the presence of liver dysfunction; therefore, we decided to continue treatment with liposomal amphotericin B alone.

Liposomal amphotericin B was continued for 4 weeks after a negative CSF culture (a total of 6 weeks; liver function improved in this time), followed by fluconazole (400 mg orally once daily) for 8 weeks as consolidation therapy, and fluconazole (200 mg orally once daily) for 1 year as maintenance therapy. She was treated for seizures with intravenous levetiracetam and fosphenytoin immediately after hospitalization, and after 5 days, treatment was switched to oral levetiracetam and lacosamide (oral clobazam was also started, but discontinued due to liver dysfunction, as described above). There was no recurrence of seizures. To treat MS, fingolimod was discontinued and replaced with an anti-CD20 monoclonal antibody, ofatumumab, because of its reliable efficacy and safety.

Discussion

Herein, we report the case of a 65-year-old woman who developed cryptococcal meningitis approximately 12 years after initiating fingolimod treatment for MS, which improved with antifungal treatment.

MS is an inflammatory-demyelinating disease of the central nervous system affecting 2.3 million people worldwide [1]. There is no curative treatment available for MS. Current therapeutic strategy aims at reducing the risk of relapses and disability progression.

Fingolimod (FTY720) is a sphingosine 1-phosphate (S1P) receptor modulator and oral DMT approved by the FDA in 2010 for the treatment of patients with relapsing–remitting MS. Fingolimod acts as an antagonist of S1P receptors on lymphocytes, inhibiting lymphocyte migration from the lymph nodes, and reducing peripheral blood lymphocyte counts. This suppresses the infiltration of autoreactive T cells into the central nervous system, which has an inhibitory effect on MS [2].

The effects of fingolimod on MS have been well-evaluated. In a Phase III study of patients with relapsing–remitting MS, fingolimod was associated with substantially lower relapse rates and less disease progression on imaging than placebo [3] and interferon beta-1a (IFNβ-1a) [4].

However, it has several adverse effects. Paradoxical worsening of MS disease activity can occur after discontinuation of fingolimod treatment at rates of 10–25 % [5]. A rapid reentry of lymphocytes into the CNS

Table 1
Clinical features and parameters of published case reports of fingolimod-associated cryptococcal meningitis with Multiple Sclerosis.

Author	Year	Age	Sex	Duration of fingolimod use	Initial symptoms	MRI findings	Serum lymphocyte (/μL)	Serum CD4 (/μL)	Serum CrAg (1: X)	CSF CrAg (1: X)	CSF opening pressure (cmH_2O)	CSF cell (/μL)	CSF lymphocyte (or mononuclear cells) (/μL)	CSF protein (mg/dL)	CSF glucose (mg/dL)	CSF culture	treatment	outcome	reference
Huang D	2015	50	Male	3y6m	headache, somnolence, nausea, ataxia	thalamic and corpus callosum lesion with mass effect, diffuse meningeal enhancement	500	ND	128	108	ND	ND	308	217	23	positive	liposomal amphotericin B + flucytosine (8w) -> fluconazole	improved	(8)
Achtnichts L	2015	40s	Male	2y	headache, photophobia, lethargy	multiple nonenhancing lesions	90	56	ND	2048	38	20	19	40	26.67	positive	liposomal amphotericin B + flucytosine (2w) -> fluconazole	improved	(9)
Ward MD	2016	67	Female	3y6m	fever, dysarthria, diplopia, vomiting, confusion, cognitive changes	multiple acute infarcts, intraparenchymal and sulcal contrast enhancement	2390	ND	40	positive	ND	ND	240	84	13	positive	amphotericin B (4w) -> fluconazole	dead	(10)
Grebenciucova E	2016	62	Male	3y	headache, dizziness, confusion	no change	336	ND	ND	positive	ND	203	ND	117	48	positive	liposomal amphotericin B + flucytosine (2w) -> fluconazole	improved	(11)
Seto H	2016	63	Male	2y	gaze palsy, facial paralysis, dysarthria, apraxia, muscle weakness, multiple cutaneous lesions	no change	300	145	256	1024	16	74	67	323	ND	negative	liposomal amphotericin B + flucytosine (6w) -> fluconazole	improved	(12)
Pham C	2017	61	Female	3y	headache, neck pain, nausea, vertigo, weight loss	leptomeningeal enhancement, fourth ventricle compression, cerebellar tonsillar herniation, obstructive hydrocephalus	120	5	positive	positive	ND	ND	ND	ND	ND	ND	liposomal amphotericin B + flucytosine (30d) -> fluconazole	improved	(13)
Anene-Maidoh TI	2018	61	Female	4y10m	headache, confusion, ataxia, seizure	nd	nd	69	positive	positive	50	48	5	91	0	positive	amphotericin B + flucytosine	dead	(14)
Chong I	2019	40	Female	2y3m	headache, generalized weakness, anorexia, hallucinations	diffuse leptomeningeal enhancement	200	ND	ND	positive	normal	22	8	142	7	positive	amphotericin B + flucytosine (6w)	improved	(15)

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Age	Sex	Duration of fingolimod use	Initial symptoms	MRI findings	Serum lymphocyte (/μL)	Serum CD4 (/μL)	Serum CrAg (1: X)	CSF CrAg (1: X)	CSF opening pressure (cmH_2O)	CSF cell (/μL)	CSF lymphocyte (or mononuclear cells) (/μL)	CSF protein (mg/dL)	CSF glucose (mg/dL)	CSF culture	treatment	outcome	reference
Kuruoglu T	2019	30	Male	5y	headache, dysarthria	ependymal surface hyperintensity, prepontine interpeduncular linear contrasts	620	192	ND	ND	ND	110	ND	114	4	positive	liposomal amphotericin B + fluconazole (4w) -> fluconazole	improved	(16)
Ma SB	2020	58	Male	7y	headache, fever, confusion	early cerebritis of bilateral parietal lobes, mild sulcal effacement, leptomeningeal enhancement	900	ND	2560	5120	29	62	62	101	40	positive	amphotericin B + flucytosine (8w) -> fluconazole	improved	(17)
Wienemann T	2020	49	Female	5y6m	headache, fever, confusion, cough. generalized weakness	no change	900	77	ND	160	normal	54	ND	146	normal	positive	liposomal amphotericin B+ fluconazole -> liposomal amphotericin B + flucytosine -> fluconazole	improved	(18)
Baghbanian SM	2020	41	Female	5y	headache, blurred vision, disorientation, meningeal signs, ataxia	intraparenchymal right occipital enhancing lesion, leptomeningeal enhancement	250	ND	ND	positive	25	20	20	30	83	positive (india ink)	amphotericin B + fluconazole (4w)	improved	(19)
Kaur P	2020	34	Male	5y	loss of consciousness, ataxia, generalized weakness, anorexia, nausea, vomiting	no change	nd	61	2560	ND	48	8	3	58.4	27	positive	liposomal amphotericin B + flucytosine (4w) -> fluconazole	improved	(20)
Cuascut FX	2021	48	Female	7y7m	headache, nausea, emesis, photophobia, phonophobia, meningismus, confusion, diplopia, seizure	leptomeningeal enhancement	210	ND	ND	1024	55	99	6	76	15	positive	amphotericin B + flucytosine -> fluconazole	improved	(21)
Aoki R	2021	41	Male	6y	headache, fever	meningeal enhancement	177	ND	2048	256	ND	65	nd	123	27	positive	liposomal amphotericin B + flucytosine (4w) -> fluconazole	improved	(22)
Darazam IA	2022	39	Female	5y	headache, fever, weakness, loss of consciousness	no change	500	ND	ND	ND	32	20	ND	normal	normal	positive	liposomal amphotericin B + flucytosine (2w) -> fluconazole	improved	(23)

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Age	Sex	Duration of fingolimod use	Initial symptoms	MRI findings	Serum lymphocyte (/μL)	Serum CD4 (/μL)	Serum CrAg (1: X)	CSF CrAg (1: X)	CSF opening pressure (cmH_2O)	CSF cell (/μL)	CSF lymphocyte (or mononuclear cells) (/μL)	CSF protein (mg/dL)	CSF glucose (mg/dL)	CSF culture	treatment	outcome	reference
Zhou DJ	2023	67	Male	6y	headache, dysphasia, ataxia, confusion	multiple parenchymal and leptomeningeal enhancement	100	ND	ND	2560	40	71	50	80	20	positive	ND	ND	(24)
Nasir M	2023	21	Female	5y	headache, photophobia, nausea, malaise	no change	530	ND	ND	100	33	< 5	ND	94	3	positive	amphotericin B + flucytosine (2w) -> fluconazole	improved	(25)
Singh R	2024	44	Male	8y	headache, ataxia, confusion, photophobia, dysphasia	leptomeningeal enhancement	250	ND	ND	ND	ND	780	218	367	3	positive	liposomal amphotericin B + flucytosine	dead	(26)
Present Case	2024	65	Female	11y11m	headache, anorexia, loss of consciousness, seizure	no change	520	ND	1024	1024	14	15	12	52	62	positive	liposomal amphotericin B + flucytosine (1w) -> liposomal amphotericin B (5w) -> fluconazole	improved	

Abbreviations: CrAg; cryptococcal antigen, CSF; cerebrospinal fluid, ND; not done or not described.

upon drug discontinuation is suggested as a possible mechanism of the "rebound" phenomenon. Fingolimod in patients with MS substantially increases the risk of infection, especially lower respiratory tract and herpes virus infections [6]. Opportunistic infections including progressive multifocal leukoencephalopathy and cryptococcal meningitis are considered rare adverse events with the use of fingolimod. *C. neoformans* infection, especially meningitis, is considered a rare adverse event of fingolimod treatment, with an estimated incidence of 8 per 100,000 patient-years (95 % confidence interval, 6.0–10.0) [7]. The exact mechanism of action of fingolimod and cryptococcal meningitis is unknown [7]. However, there are multiple case reports of fingolimod-associated cryptococcal meningitis in MS patients since 2015.

A literature review (as of 2024) revealed 19 case reports of cryptococcal meningitis in MS patients treated with fingolimod. Table 1 shows the clinical characteristics of the 20 patients, including this case [8–26]. Of the 20 patients, equal numbers of male and female cases were reported. The median patient age was 49 years (n = 19, range 21–67 years old), and the present case was the third-oldest. The median duration of fingolimod treatment was 5 years, and the present case developed cryptococcal meningitis after the longest period following the initiation of fingolimod treatment. The risk of cryptococcal meningitis tends to increase with the duration of fingolimod treatment; however, no definitive conclusions have been made [7]. Headache was the most common initial symptom in 85 % (17/20) of the patients; only 25 % (5/20) developed fever. Contrast-enhanced brain MRI indicated leptomeningeal enhancement in 47 % (9/19) of patients, consistent with cryptococcal meningitis, whereas 42 % (8/19) of patients had no new lesions (including the present case). The median serum lymphocyte and CD4-positive lymphocyte counts (at the time of cryptococcal meningitis diagnosis) both declined to 318/μL (n = 18, range 90–2390/μL) and 69/μL (n = 7, range 5–192/μL), respectively.

CSF findings include intracranial pressure greater than 25 cmH_2O in 9 cases (median 33 cmH_2O, range 25–55 cmH_2O), whereas in the remaining 4 cases it was normal. CSF cells were only mildly elevated, with a median of 58/μL (n = 16). CSF protein concentration was elevated over 45 mg/dL in 16 out of 18 cases where specific values were given (median 97.5 mg/dL, range 30–367 mg/dL). CSF glucose concentration was reduced to median 21.5 mg/dL (n = 16). Cryptococcal antigen testing of serum or CSF was always positive if tested (n = 17). The fungal culture of CSF was positive for *C. neoformans* in all but one case. Most patients are treated with amphotericin B (liposomal or non-liposomal) and/or flucytosine as induction therapy, followed by fluconazole as consolidation and maintenance therapy. Although a minimal 2-week induction therapy for cryptococcal meningitis in non-HIV patients is recommended [27], it has been reported that induction therapy for 6 weeks is associated with a lower risk of relapse when neurological complications (e.g., seizures) developed [28], as in the present case. The recommended durations of consolidation and maintenance therapies are 8 weeks and 12 months, respectively [27]. The mortality rate was 16 % (3/19), which was the similar to or lower than in the previous studies on cryptococcosis-related mortality in various populations [29].

Fingolimod-associated cryptococcal meningitis is a rare but potentially lethal infection if the diagnosis is delayed. Symptoms may be subtle and brain MRI may not show significant changes. A prompt diagnostic evaluation including lumber puncture is required; intracranial pressure is typically elevated. CNS lymphocyte elevation may be mild due to fingolimod. CNS fungal culture, which remains the standard method of diagnosis, is limited by prolonged time of organism growth. CSF cryptococcal antigen testing can be rapidly performed with high sensitivity and specificity. Treatment may take months to complete.

Consent

Written informed consent for publishing the case report was obtained from the patient.

Ethical approval

Written informed consent for publication was obtained from each participant, and ethical approval was waived.

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CRediT authorship contribution statement

Hidenori Nakagawa: Writing – original draft, Conceptualization. **Michinori Shirano:** Writing – review & editing, Supervision. **Takahiro Mitsueda:** Writing – review & editing. **Akari Takagi:** Writing – review & editing.

Declaration of Competing Interest

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

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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