

การติดเชื้อราคริปโตคอคคัสที่เยื่อหุ้มสมองและในกระแสเลือดผู้ป่วยโรคปอดประสาทเสื่อมแข็งที่ได้รับยาฟิงโกลิมิด: รายงานผู้ป่วย 1 ราย

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บทคัดย่อ

โรคปอดประสาทเสื่อมแข็งเป็นโรคที่พบบ่อยในระบบประสาทส่วนกลางของมนุษย์ และทำให้เกิดความพิการทางระบบประสาท ยาฟิงโกลิมิดเป็นยาแบบรับประทานตัวแรกโดยออกฤทธิ์ที่ตำแหน่ง sphingosine-1-phosphate receptor ใช้ป้องกันการกลับเป็นซ้ำของโรคปอดประสาทเสื่อมแข็ง กลไกของยาคือลดจำนวนเม็ดเลือดขาวลิมโฟไซต์จากต่อมน้ำเหลืองไปยังระบบประสาทส่วนกลางจึงเกิดภาวะเม็ดเลือดขาวในเลือดต่ำ ซึ่งเสี่ยงต่อการติดเชื้อฉวยโอกาสได้ ชายอายุ 34 ปีได้รับการวินิจฉัยว่าเป็นโรคปอดประสาทเสื่อมแข็งในปี พ.ศ. 2560 จากการมีเดินเกร็งและขาอ่อนแรง โดยมีอาการเริ่มแรกเป็นการสูญเสียการมองเห็นเฉียบพลันโดยเป็นการสูญเสียการมองเห็นครึ่งซีกทางด้านซ้ายในปี พ.ศ. 2556 เริ่มการรักษาการกลับเป็นซ้ำของโรคปอดประสาทเสื่อมแข็งในปี พ.ศ. 2560 และรักษาด้วยการใช้ยาฟิงโกลิมิดในเดือนกันยายน พ.ศ. 2562 เนื่องจากมีการกำเริบซ้ำของโรค ประมาณ 4 ปีหลังจากเริ่มใช้ยา เขามีอาการปวดศีรษะและปวดต่อนกรอกตาอย่างรุนแรง และเห็นภาพมัว ไม่ชัดเจน ครั้งแรกวินิจฉัยเป็นปอดประสาทเสื่อมแข็งที่มีการอักเสบซ้ำ ให้ยาเมทิลเพรดนิโซโลนขนาดสูง มีอาการดีขึ้นเล็กน้อยปวดศีรษะและตามัวลดลง หลังจากนั้นสองสัปดาห์กลับมาที่โรงพยาบาลซ้ำด้วยอาการซึมและสับสน ตรวจรักษาและวินิจฉัยใหม่เป็นติดเชื้อคริปโตคอคคัสแบบกระจายทั่วร่างกาย จากการเพาะเชื้อในเลือดและน้ำไขสันหลัง โดยตรวจพบ *Cryptococcus Neoformans* ผู้ป่วยได้รับการรักษาด้วยยาต้านเชื้อราตามมาตรฐาน Amphotericin B และ flucytosine และได้เปลี่ยนเป็น Liposomal amphotericin B และ fluconazole จากอาการปวดศีรษะมากขึ้นและมีไตวายเฉียบพลัน เจาะระบายน้ำไขสันหลังวันเว้นวันเพื่อลดแรงดันในสมอง หลังจากนั้น 2 สัปดาห์มีอาการดีขึ้น

คำสำคัญ: ติดเชื้อคริปโตคอคคัส; ฟิงโกลิมิด; โรคปอดประสาทเสื่อมแข็ง

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Cryptococcal meningitis with cryptococemia in a multiple sclerosis patient treated with Fingolimod: A case report

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Abstract

Multiple sclerosis (MS) is one of the most common diseases of the human central nervous system, causing significant neurological disability. Fingolimod, a sphingosine-1-phosphate receptor modulator, is an approved oral therapy for relapsing-remitting multiple sclerosis (RRMS) that works by decreasing the egress of lymphocytes from lymph nodes to the central nervous system. Despite its effectiveness in treating MS, Fingolimod can increase the risk of opportunistic infections due to its immunosuppressive effects. A 34-year-old male was diagnosed with MS in 2017, presenting with spastic gait, paraparesis, and a history of left homonymous hemianopia. He was prescribed Fingolimod in September 2019 following a relapse. About four years after starting Fingolimod, he developed severe headaches and visual impairment. Initially treated for an MS relapse with methylprednisolone, he returned two weeks later with progressive loss of consciousness and confusion, and was subsequently diagnosed with disseminated cryptococcosis. Hemoculture and cerebrospinal fluid culture confirmed the presence of *Cryptococcus neoformans*. Due to clinical worsening and acute renal injury, the patient was treated with liposomal amphotericin B and fluconazole, after receiving routine induction therapy with amphotericin B and flucytosine. The patient underwent serial lumbar punctures every other day for intracranial pressure management. After two weeks of treatment, he was discharged with significant improvement and no major complaints.

Keywords: cryptococcosis; fingolimod; multiple sclerosis

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system primarily the brain, spinal cord, and optic nerves. In MS, the immune system mistakenly attacks the protective myelin sheath that covers nerve fibers, leading to inflammation, demyelination, and eventual scarring from gliosis and neurodegeneration¹. MS can present with a wide variety of symptoms, depending on which areas of the CNS are affected, include vision problems, numbness or tingling in limbs, weakness in limbs, balance and coordination problems, cognitive dysfunction, and bladder dysfunction. The current diagnosis and disease course were determined following the 2017 revised McDonald criteria². These criteria emphasize the need to demonstrate evidence of lesions in different areas of the central nervous system (2 in 4 lesions: periventricular, juxtacortical, infratentorial, or spinal cord) by the presence of 1 or more T2 hyperintense lesions on MRI, indicating dissemination in space (DIS). Evidence that lesions occurred at different is shown by a new T2 hyperintense or gadolinium-enhancing lesion on MRI compared to a previous scan, regardless of the timing, or by the presence of CSF-specific oligoclonal bands, which indicate an immune response over time, called dissemination in time (DIT). MS is diagnosed based on the presence of DIS and DIT. Patients with a first episode not meeting these criteria are classified as having clinically isolated syndrome (CIS). MS is categorized into two main types: relapsing-

remitting MS (RRMS) and primary progressive MS (PPMS). RRMS is the most common type, characterized by relapses followed by periods of remission. About 80% of RRMS patients transition to secondary progressive MS (SPMS) after 10-15 years. PPMS is characterized by a continuous worsening of disability from onset for at least 1 year without relapses, affecting approximately 15% of MS patients.

The main objectives of MS treatment are to control inflammation and myelin damage, prevent relapses, and slow disability progression. Disease-Modifying Therapies (DMTs) are used to treat RRMS and are classified into two categories: highly effective therapies and modestly effective therapies. The choice of therapy depends on the frequency of relapses, disease activity, drug properties, patient comorbidities, risk of side effects, and response to previous treatments. For patients with fewer relapses and/or less disease activity, treatment often begins with modestly effective therapies such as interferon (IFN)-beta and glatiramer acetate (GA).

Fingolimod, a sphingosine-1-phosphate receptor modulator, is an approved oral DMT for RRMS that was first approved by the U.S. Food and Drug Administration (FDA) on September 21, 2010³ and by Thai Food and Drug Administration on July 18, 2012⁴ as highly effective therapies. Fingolimod limits the ability of lymphocytes, especially naïve T cells and central memory T cells, to transmigrate across the blood-brain barrier and induce CNS inflammation from lymph nodes⁵. This pharmacologic activity increases the risk of

opportunistic infections, including fungal and viral infections. *Cryptococcus neoformans* is an encapsulated fungus that commonly causes meningitis and occasionally cryptococcosis. Although, this organism can be pathogenesis in either, immunocompetent or immunocompromised host, it usually affects immunocompromised host such as symptomatic HIV patients and patients receiving chemotherapy.

Disseminated cryptococcosis, characterized by the multiple organ infections after an event of fungemia and is uncommon in patients treated with Fingolimod. We report a case of disseminated cryptococcosis in a patient with RRMS treated with Fingolimod in Thailand.

Case report

A 34-year-old man initially presented with acute visual loss (left homonymous hemianopia) in 2013 but did not go to the hospital and did not receive any medication treatment; he self-improved. He was later diagnosed with multiple sclerosis in 2017 after presenting with chronic progressive paraparesis and spastic gait over three months, along with progressive motor weakness that developed within one week. Follow-up MRI of the brain and screening of the entire spine showed

hyperintense signal intensity on T2-weighted images at the T8-T9 level and an old lesion in the right parieto-occipital lobe (Figure 1A). The presence of oligoclonal bands in the cerebrospinal fluid (CSF) and their absence in serum meet the McDonald criteria for the diagnosis of multiple sclerosis. The serologic tests of NMOs-IgG were negative in serum and CSF. He was prescribed intravenous methylprednisolone for acute management, along with a continuous regimen of oral prednisolone at 20 mg per day. Fingolimod was started in September 2019 due to relapse symptoms, including leg weakness, progressive spasticity, and numbness. A follow-up MRI of the spine revealed a new lesion in the T2-weighted series, with gadolinium enhancement at the C2 spinal cord level (Figure 1B), leading to a diagnosis of aggressive RRMS. After follow-up, his symptoms did not present any other complications, such as abnormal vision, hepatitis, or increased liver transaminase levels. His absolute lymphocyte count was between 300 and 500 cells/ μ L after starting Fingolimod, which precluded further brain magnetic resonance imaging (MRI) scans and spinal imaging. This follow-up monitored his symptoms of spastic gait and leg weakness between 2019 and 2023.

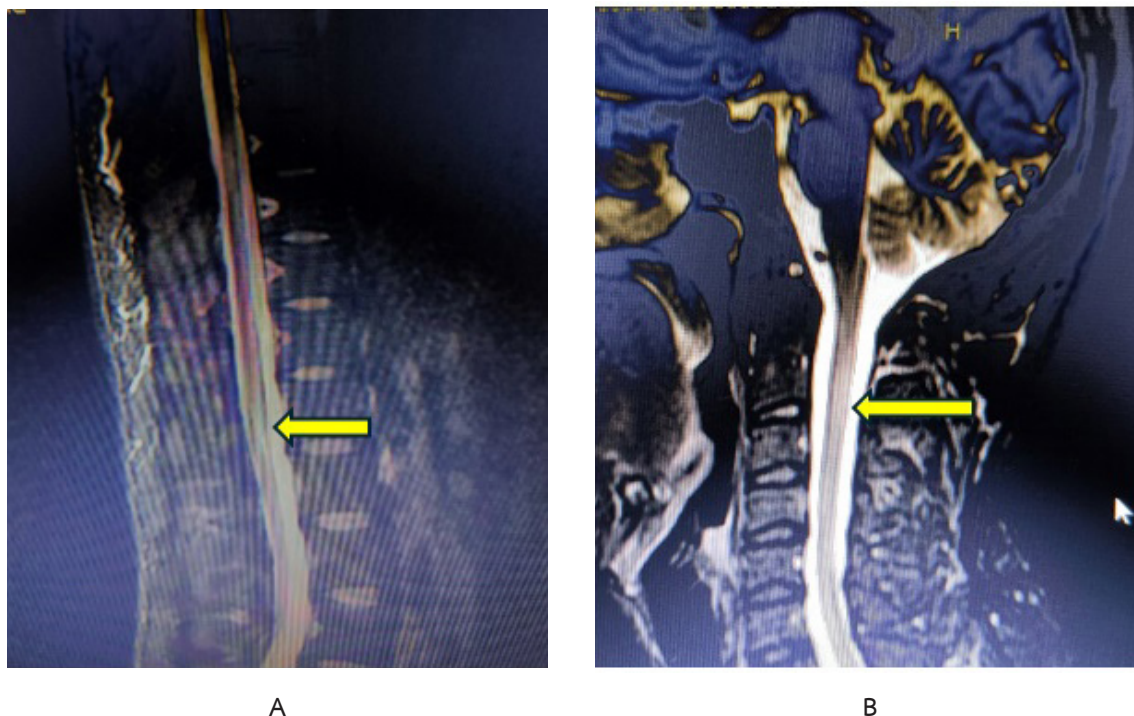


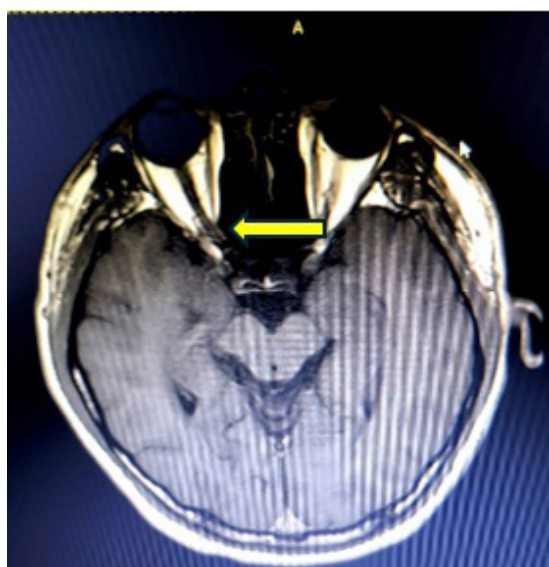
Figure 1 A: MRI spine show hypersignal showed hyperintense signal intensity on T2-weighted images at the T8-T9 level in 2017 B: MRI c-spine show T2-weighted series with gadolinium enhancement at the C2 spinal cord level in 2019 (indicated by the yellow arrow).

In November 2023, after receive Fingolimods 4 years and oral dexamethasone 2 mg/day. He presented with a severe headache, bilateral eye pain when moving his eyes, and blurred vision, He was afebrile. There was no nuchal rigidity. Visual acuity left side 20/20 and right side 20/30, Neurologic examination showed reduced sensation on bilateral lower extremities, which was unchanged as compared to findings from his previous physical examinations. A CT brain was normal, while the T2/FLAIR MRI of the brain show hypersignal intensities along the right optic tract (posterior aspect) (Figure 2A) and right temporo-occipital white matter (Figure 2B), involving right optic radiation

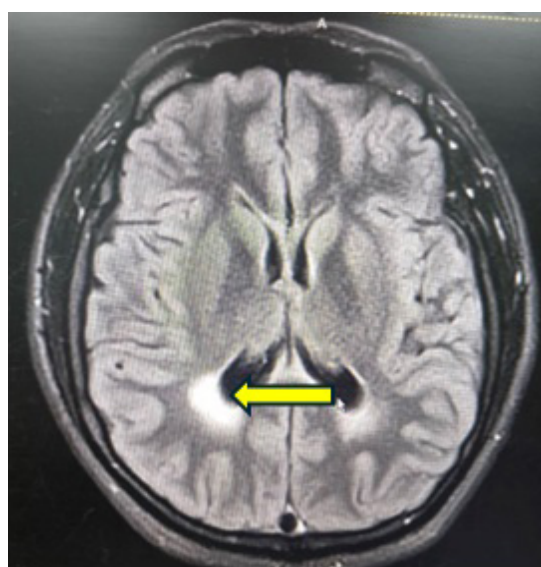
leading to a provisional diagnosis of RRMS. He was treated with 1 gram of methylprednisolone for 5 days. His clinical symptoms improved within a week, and he was discharged from the ward. However, two weeks later, he was brought back to the hospital due to an alteration of consciousness. The initial neurologic examination revealed neck stiffness and a Glasgow Coma Scale (GCS) score of 10 (eye opening to sound, confusion, and abnormal flexion to pain). A CT brain scan was normal, showing no evidence of stroke, vasculitis, or mass lesions. A lumbar puncture (LP) was performed, revealing an elevated opening pressure of 400 mmH₂O. Cerebrospinal fluid (CSF) analysis showed lymphocytic pleocytosis

(WBC count of 27 cells, with neutrophils at 7%, lymphocytes at 43%, and monocytes at 50%), elevated protein levels (61.9 mg/dL), and low glucose levels (33 mg/dL). Cryptococcal antigen was detected in both peripheral blood and CSF. The CSF Indian ink preparation revealed a few encapsulated budding yeasts,

and fungal cultures from both CSF and blood were positive for *Cryptococcus neoformans*, while other causes of meningoencephalitis, including herpes viruses, bacteria, and tuberculosis, were excluded. The serologic test for HIV was negative. He was diagnosed with Cryptococcal meningitis with cryptococcemia.



A



B

Figure 2 MRI brain show hypersignal intensities along the right optic tract (posterior aspect) (A) and right temporo-occipital white matter (B) (indicated by the yellow arrow).

Amphotericin B and flucytosine were prescribed as induction therapies. steroid and Fingolimod administration was discontinued. The patient underwent repeated lumbar punctures on alternating days to relieve intracranial pressure through high-volume drainage. An initial head computed tomography (CT) scan showed an old hypodense lesion in the right parieto-occipital lobe. Over the next four days, he experienced a progressive

decline in consciousness, and an MRI brain scan revealed findings similar to those of the initial CT, suggesting an old lesion associated with left homonymous hemianopia. In addition to spinal taps that released 15 ml of CSF every other day until the opening pressure was below 200 mmH₂O, liposomal amphotericin B and fluconazole were prescribed as an alternative regimen due to the failure of the first regimen and acute kidney injury. Two

weeks later, the patient showed clinical improvement and was discharged.

Discussion

The 34-year-old male was diagnosed with multiple sclerosis (MS) in 2017, as described by the McDonald criteria. This diagnosis was supported by evidence of lesions in the parieto-occipital region (juxtacortical) and spinal cord, indicating dissemination in space (DIS). There was also evidence that lesions occurred at different times, including a T2W hyperintense lesion in the parieto-occipital lobe in 2013, a T2W hyperintense lesion at the T8-T9 level of the spinal cord in 2017, and lesion in T2W and gadolinium enhancement at the C2 spinal cord level in 2019, which indicates dissemination in time (DIT). The serologic test for oligoclonal bands was positive in the cerebrospinal fluid (CSF) and negative in serum. Additionally, NMOS-IgG was negative in both serum and CSF. Many studies have suggested that male sex influences poor long-term disability outcomes and is associated with aggressive relapsing-remitting MS (RRMS), which is similar to this case⁶. The presence of infratentorial lesions is also associated with future disability accumulation in clinically isolated syndrome (CIS) or MS; this is evident here, as the patient accumulated T2-weighted lesions at the cervical and thoracic levels, leading to increased disability. In this case, treatment management was inadequate after the diagnosis of RRMS in 2017. The patient received intravenous methylprednisolone

followed by oral prednisolone but did not receive disease-modifying therapy (DMT). Given that he had infratentorial lesions, which carry a higher risk for relapse and disease progression, this lack of appropriate management may have contributed to his clinical course⁷.

Fingolimod is a Sphingosine 1-phosphate (S1P) receptor modulator is authorized for the treatment of multiple sclerosis in individual of all ages. Fingolimod reduces the amount of lymphocytes that enter the central nervous system from lymph nodes and downregulates the expression of S1P receptors on lymphocytes. It also lessens the activity of multiple sclerosis disease. Those results lead to peripheral lymphopenia⁸. No association was observed between the nadir in lymphocyte count and the incidence of the most common infections in the clinical trials of Fingolimod in patients with multiple sclerosis⁹⁻¹⁰. This may select only naïve T cells and central memory cells in the lymph nodes and selective sparing of effector memory T cells by Fingolimod. The opportunistic infections reported in patients treated with Fingolimod include viral and fungal infections, such as JC virus and cryptococcal infection¹¹. The exact relationship between the mechanism of action of Fingolimod and cryptococcal infections is not known¹². This patient's absolute lymphocyte count was between 300 and 500 cells/ μ L between follow-up, not increasing his susceptibility to opportunistic infections. However, a report indicates that a lymphocyte counts below 200 cells/ μ L is associated with herpes infections¹³.

Cryptococcus neoformans is the most common cause of fungal infection in humans, and it occurs in immunocompromised patients^{12,14}. The most common form of cryptococcal infection is cryptococcal meningitis, which presents with neurological symptoms, most typically headaches, fevers, and altered mental status¹⁵. Cryptococcal meningitis in patients with multiple sclerosis who present with nonspecific neurological symptoms, such as headaches and bilateral eye pain when moving their eyes, may lead to missed diagnoses and serious consequences due to delayed recognition of the condition, similar in this case. Cryptococcal meningitis were treated with Fingolimod based on 60 cases was identified¹⁶. Because it is a rare event, the initial symptoms could be mistaken for an MS relapse or other neurological conditions. This case emphasizes the importance of considering opportunistic infections in MS patients on immunosuppressive therapies.

Conclusion

Fingolimod-associated disseminated cryptococcosis is a rare event. Fingolimod therapy in patients with multiple sclerosis should be performed cautiously¹⁷. Regular follow-ups may give rise to a timely diagnosis of a probable Fingolimod-associated cryptococcal infection. Fingolimod treatment can lead to lymphopenia and a risk of opportunistic infection. Therefore, we suggest

that intermittent blood lymphocyte counts as well as monitoring of clinical manifestations among multiple sclerosis patients who take Fingolimod be performed in order to avoid risk for opportunistic infection¹⁸. While Fingolimod is an effective treatment for MS, this case highlights the need for careful consideration of its risks, particularly in terms of opportunistic infections.

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Conflicts of interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

References

1. Tafti D, Ehsan M, Xixis KL. Multiple sclerosis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls publishing; 2024 [cited 2024 Mar 8]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK499849/>.
2. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17:162-73. doi:10.1016/S1474-4422(17)30470-2.
3. Sharma S, Mathur AG, Pradhan S, et al. Fingolimod (FTY720): First approved oral therapy for multiple sclerosis. *J Pharmacol Pharmacother* 2011;2:49-51. doi:10.4103/0976-500X.77118.

4. Pertento.fda.moph.go.th. [Internet]. [cited 2024 Sep 6]. Available from: https://pertento.fda.moph.go.th/FDA_SEARCH_DRUG/SEARCH_DRUG/FRM_SEARCH_DRUG.aspx. (in Thai)
5. Kappos L, Antel J, Comi G, et al. Oral Fingolimod (FTY720) for Relapsing Multiple Sclerosis. *N Engl J Med* 2006;355:1124-40. doi:10.1056/NEJMoa052643.
6. Renoux C. Natural history of multiple sclerosis: Long-term prognostic factors. *Neurol Clin* 2011;29:293-308. doi:10.1016/j.ncl.2011.01.006.
7. Minneboo A, Barkhof F, Polman CH, et al. Infratentorial lesions predict long-term disability in patients with initial findings suggestive of multiple sclerosis. *Arch Neurol* 2004;61:217-21. doi:10.1001/archneur.61.2.217.
8. Grebenciucova E, Reder AT, Bernard JT. Immunologic mechanisms of Fingolimod and the role of immunosenescence in the risk of cryptococcal infection: A case report and review of literature. *Mult Scler Relat Disord* 2016;9:158-62. doi:10.1016/j.msard.2016.07.015.
9. Handley G, Hand J. Adverse Effects of Immunosuppression: Infections. *Handb Exp Pharmacol* 2022;272:287-314. doi:10.1007/164_2021_550.
10. Jalkh G, Abi Nahed R, Macaron G, et al. Safety of newer disease modifying therapies in multiple sclerosis. *Vaccines (Basel)* 2020;9:12. doi:10.3390/vaccines9010012.
11. Carpenter K, Etemady-Deylami A, Costello V, et al. Cryptococcal chest wall mass and rib osteomyelitis associated with the use of Fingolimod: A case report and literature review. *Front Med (Lausanne)* 2022;9:942751. doi:10.3389/fmed.2022.942751.
12. US Food and Drug Administration. (2012). Gilenya prescribing information. [Internet]. 2012 [cited 2024 Sep 6]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022527s006lbl.pdf.
13. Francis G, Kappos L, O'Connor P, et al. Temporal profile of lymphocyte counts and relationship with infections with Fingolimod therapy. *Mult Scler* 2014;20:471-80. doi:10.1177/1352458513500551.
14. Aoki R, Mori M, Suzuki YI, et al. Cryptococcal Meningitis in a Fingolimod-treated patient: Positive antigen test a year before onset. *Neurol Clin Pract* 2021;11:e549-50. doi:10.1212/CPJ.0000000000001051.
15. Anene-Maidoh TI, Paschall RM, Scott Graham R. Refractory cryptococcal meningoencephalitis in a patient with multiple sclerosis treated with Fingolimod: A case report. *Interdiscip Neurosurg*. 2018; 12:8-9. doi:10.1016/j.inat.2017.10.005.
16. Del Poeta M, Ward BJ, Greenberg B, et al. Cryptococcal meningitis reported with Fingolimod treatment: Case series. *Neurol Neuroimmunol Neuroinflamm* 2022;9:e1156. doi:10.1212/NXI.0000000000001156.

17. Wienemann T, Müller AK, MacKenzie C, et al. Cryptococcal meningoencephalitis in an IgG2-deficient patient with multiple sclerosis on Fingolimod therapy for more than five years - case report. *BMC Neurol* 2020;20:158. doi:10.1186/s12883-020-01741-0.
18. Dobson R, Giovannoni G. Multiple sclerosis - a review. *Eur J Neurol* 2019;26: 27-40. doi:10.1111/ene.13819.