



## Case Report

# Cryptococcal Meningitis in a Patient with Multiple Sclerosis Treated with Fingolimod: A Case Report

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## Abstract

**Background:** Fingolimod is an oral medication approved by the Food and Drug Administration for the treatment of Relapsing Remitting Multiple Sclerosis (RRMS). Integrated analysis of the long-term safety studies results showed that there was no overall increase in the risk of infection in patients treated with fingolimod compared to patients treated with placebo. However, fingolimod may be associated with a higher risk of several different opportunistic infections, including cryptococcosis. Post-marketing experience has documented several cases of cryptococcal meningitis and disseminated cryptococcosis. Early diagnosis and appropriate treatment are essential to improve prognosis and reduce mortality in these cases. **Case presentation:** We present a 46-year old woman with RRMS on fingolimod therapy with a rare case of cryptococcal meningitis. She was reported to the hospital emergency department due to headache with accompanying low-grade fever. She was diagnosed with RRMS in 1998. She has been treated with fingolimod since 2013. The results of laboratory and imaging tests were inconclusive. Examination of Cerebrospinal Fluid (CSF) showed intensified cytosis, increased protein level and decreased glucose level. In Magnetic Resonance Imaging (MRI) strengthening of the meninges of the brain and cerebellum was visualized. Finally, a culture of the CSF showed *Cryptococcus neoformans* growth. Cryptococcal meningitis has been recognized. Amphotericin B with fluconazole were included and fingolimod was discontinued. The patient's general and neurological condition gradually improved. In the control examination, CSF culture showed no microbial growth and MRI showed an improvement in the radiological condition. **Conclusion:** Some agents carry a risk of opportunistic and life-threatening infections. Recommendations for the surveillance of opportunistic infections are increasingly needed as more patients are treated with immunomodulation therapy for longer durations and at older ages. In this report, we present the treatment problems that arise in patients with MS treated with immunomodulation therapy who develop an opportunistic infection.

**Keywords:** Fingolimod; Cryptococcal meningitis; Multiple sclerosis; Disease-modifying therapies

**Abbreviations:** MS: Multiple Sclerosis; CNS: Central Nervous System; DMTs: Disease-Modifying Therapies; S1P: Sphingosine-1-Phosphate; RRMS: Relapsing-Remitting MS; PML: Progressive Multifocal Leukoencephalopathy; HSV: Herpes Simplex Virus; CSF: Cerebrospinal Fluid; MRI: Magnetic Resonance Imaging;

MRC: Medical Research Council; CRP: C-Reactive Protein; INF: Interferon; AIDS: Acquired Immunodeficiency Syndrome; IRIS: Immune Reconstitution Inflammatory Responses

## Introduction

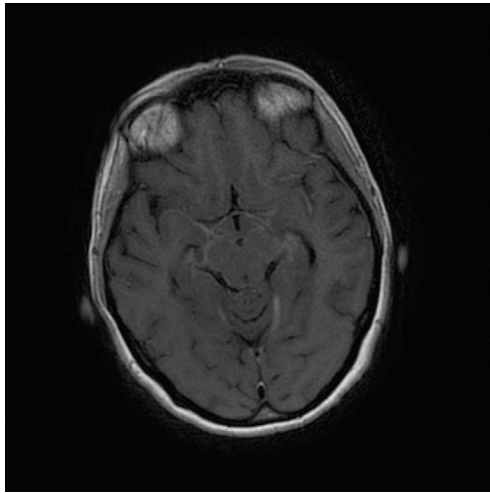
Multiple Sclerosis (MS), the most common neurological disability, is an autoimmune disorder that affects the Central Nervous System (CNS) and often leads to severe physical

or cognitive dysfunctions in young adults [1]. This chronic inflammatory condition of the CNS is caused by an autoimmune process, leading to multifocal demyelination and axonal loss, mostly in the white matter, but importantly also in the grey matter of both brain and spinal cord. Currently approved Disease-Modifying Therapies (DMTs) are immunomodulatory or immunosuppressive drugs that significantly, although variably, reduce the frequency of attacks of the relapsing forms of the disease [2]. Most drugs used in MS treatment are linked to an increased risk of infection to varying degrees, depending on their mechanism of action [3]. As the number of treatment-related infections is increasing, careful diagnosis of MS patients presenting with new neurological symptoms is essential. Fingolimod, a first-in-class Sphingosine-1-Phosphate (S1P) receptor modulator was the first oral drug to be approved for the treatment of MS [3]. It was indicated as a DMT for the treatment of adult patients and pediatric patients of 10 years of age and above with RRMS to reduce the frequency of relapses and to delay the progression of disability. The binding of the S1P receptor on T lymphocytes blocks their migration from the lymph nodes to the CNS. The most common side effects of fingolimod are cold, headache, increased gamma-glutamyl transfer, diarrhea, nausea, abdominal pain and fatigue [4]. The effect of fingolimod on the immune system may increase the risk of infections, including opportunistic infections such as Progressive Multifocal Leukoencephalopathy [PML], recurrent or disseminated Herpes Simplex Virus (HSV) infections, and fungal infections. Since 2015, post-marketing experience has documented several cases of cryptococcal meningitis and disseminated cryptococcosis associated with the use of fingolimod [4]. We present a case of cryptococcal meningitis in a patient treated with fingolimod. The purpose of this article is to emphasize the importance of appropriate use of DMTs in MS patients during the treatment of an opportunistic infection associated with this therapy.

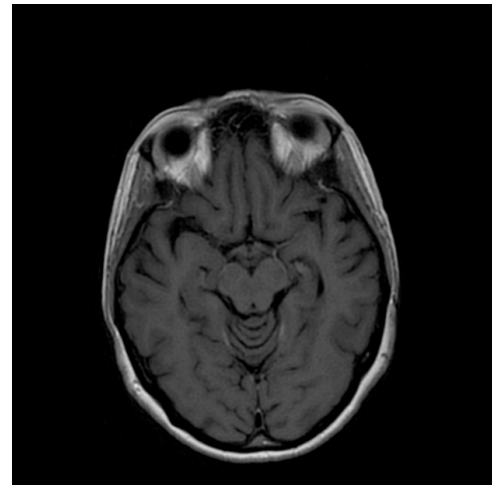
## Case Presentation

In July 2020 a 46-year-old patient was reported to the hospital emergency department of the Military Institute of Warsaw due to headache lasting for a month with additionally low-grade fever for a week (temperature at admission was 38.3 Celsius degree). She has been presented bilateral, pulsating headache in the temporal and occipital areas. Pain has not been associated with fatigue effort and has had no obvious trigger factor. Woman denied nausea, vomiting,

sensitivity to light and sounds. She has had a negative interview in the direction of the tick bite and previous infections. She also had a negative COVID-19 history. The patient was diagnosed and symptomatically treated outpatient for rhinitis and trigeminal / suboccipital neuralgia. She had felt a temporary improvement after taking a nonsteroidal anti-inflammatory drug. In 1998, the patient was diagnosed with multiple sclerosis. She was initially treated with interferon, subsequently with fingolimod (Gilenya) between 2013 and 2020. She was clinically and radiologically stable. There were no relapses. The patient was under the care of the Neurological Clinic of the Ministry of Interior and Administration. In addition, her medical history included arterial hypertension. In neurological examination meningeal symptoms were absent and cranial nerves were unchanged. Left hemiparesis in the left upper extremity (4 + / 5 in Medical Research Council (MRC) scale) and in the left lower extremity (4- / 5 MRC), increased muscle tension in the lower extremities, excessed tendon reflexes in the lower extremities, very lively tendon reflexes in the upper extremities and tendency to Babinski's symptom on the left side were observed. There were no abdominal reflexes and no sensory disturbances. Dysmetria in the cerebellar tests with advantage to the left side was observed. Unstable Romberg's test and periodic urinary incontinence were also noticed. Free walking distance was about 50 meters. For longer distances the patient was walking using a walking stick. Results of laboratory tests showed lymphopenia (without leukopenia), while markers of inflammation were not elevated and urinalysis was normal. Lumbar puncture was obtained receiving a clear CSF with cytosis of 244 cells, lymphocytic smear 79.6%, elevated level of protein and reduced level of glucose. The CSF synthesis was significantly increased, while the CSF index was normal. Due to the inconclusive results of the CSF study, antiviral treatment (acyclovir 3x750 mg intravenous) and antibacterial treatment (ceftriaxone 2x1 g intravenous) were empirically initiated and fingolimod was discontinued. Temporary improvement (fever and headache disappeared) was observed. From the fourth day of hospitalization increasing pressure headache on both sides in the behind-the-ear area appeared. They were accompanied by a feeling of scalp hyperalgesia in the parieto-temporal area. Fever was not noticed. On the seventh day of hospitalization, after one episode of vomiting, speech disorders by a significant degree of the nature of mixed aphasia with accompanying disturbances of consciousness suddenly appeared.



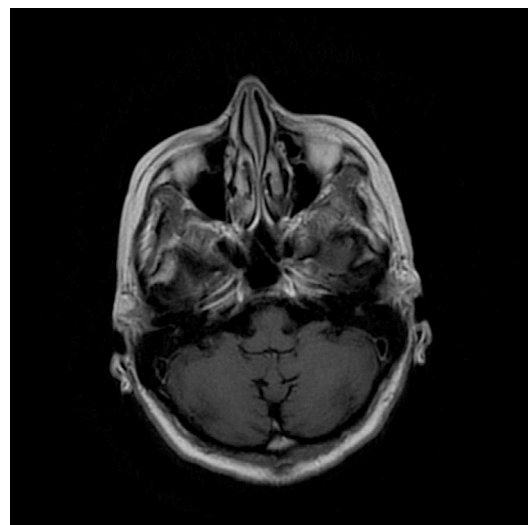
**Figure 1:** MRI of the brain in T1-weighted images after administration of an IV contrast agent. Visible strengthening and thickening of the meninges at the base of the skull.



**Figure 3:** MRI of the brain in T1-weighted images after administration of an IV contrast agent. The regression of strengthening and thickening of the meninges at the skull base was observed.



**Figure 2:** MRI of the cerebellum in T1-weighted images after administration of an IV contrast agent. Visible strengthening and thickening of the meninges at the base of the skull.



**Figure 4:** MRI of the cerebellum in T1-weighted images after administration of an IV contrast agent. The regression of strengthening and thickening of the meninges at the skull base was observed.

Results of control laboratory tests showed lymphopenia, while level of C-reactive protein (CRP =1.8 mg/l) and ionogram were normal. Lumbar puncture was repeated. CSF examination showed cytosis with 133 cells and lymphocytic smear 59.6%, increased protein level and decreased glucose level. Magnetic Resonance Imaging (MRI) was performed. After intravenous administration of a contrast agent, strengthening of the meninges of the brain and cerebellum was visualized. The changes were most severe at the base of the brain and in the area of the left hemisphere (Figure 1). In both hemispheres of the brain, various sizes, local confluent increased signal foci in T2-weighted images were found. Changes of a similar nature were observed in the corpus callosum, in the brainstem and in the middle cerebellar limb on the left side (Figure 2). Moreover, massive hyperostosis of the inner lamina of the frontal bone was visualized. In the treatment Vancomycin, intravenous glucocorticosteroids at a dose of 24 mg daily and intravenous valproic acid were included. The patient's condition was stabilized. The patient was suspected of exacerbation of inflammatory lesions of the central nervous system or immune Reconstitution Inflammatory Responses (IRIS) in the setting of progressive PML. The CSF culture was a breakthrough in diagnostics due to the detection of *Cryptococcus neoformans*. Consequently, Cryptococcal meningitis has been recognized. The treatment regimen was consulted with an infectious diseases doctor. It was decided to start treatment in the regimen used in opportunistic infections (including cryptococcal meningitis) in immunocompromised patients. The current antiviral and antibacterial treatment was discontinued. Amphotericin B (liposomal form) was started at a dose of 15 mg per 1 kilo of body weight for 14 days with fluconazole in a decreasing dose, initially 800 mg. A gradual improvement in the general and neurological condition of the patient was observed. The disturbance of consciousness, headache and speech disorders disappeared. Control CSF examination after 14 days of treatment showed cytosis with 46 cells and lymphocytic smear 96.9%. Glucose level was normal, while protein level was slightly elevated. Index and CSF synthesis were normal. Control MRI with contrast showed an improvement in the radiological condition and less severe features of the meninges strengthening (Figures 3 and 4). The patient was discharged to the home in good general condition. In the control examination, performed in October 2020, CSF was clear with cytosis of 49 cells (96.7% lymphocytes in the smear), decreased level of glucose, slightly elevated level of protein, and normal CSF index and IgG synthesis. CSF culture showed no microbial growth. During hospitalization, the patient reported neuralgia in the trigeminal nerve on the left side. Pregabalin was included in the treatment. The patient's symptoms disappeared. Since the onset of cryptococcal meningitis, the patient remains untreated for MS. The patient experienced one mild relapse during this time. This case was reported to the manufacturer of Gilenya.

## Discussion and Conclusion

Fungal meningitis is a rare complication of immunomodulating treatment in MS. Single cases of patients with cryptococcal meningitis after treatment with fingolimod have been published in the world literature. The presented case is the first one reported in Poland. All reported cases have been after approximately 2 to 3 years of taking fingolimod, although the exact relationship with the duration of treatment is unknown. In addition, an appropriate control system opportunistic infection and management regimen for active infection in a patient with demyelinating disease has not yet been developed. Cryptococcal meningitis is associated with high mortality and morbidity [5]. Therefore, patients with symptoms and signs indicative of cryptococcal meningitis should undergo a thorough diagnosis as soon as possible. Early diagnosis and appropriate treatment are essential to improve prognosis and reduce mortality. There have also been reports of disseminated cryptococcosis and primary cutaneous *Cryptococcus* with or without neurological symptoms [6-9]. Similarly, early diagnosis and antifungal treatment are critical in these cases to improve treatment outcomes. Fingolimod treatment was discontinued in the majority of reported cases of cryptococcal infections. The long-term effects of fingolimod have been assessed in studies such as FREEDOMS, FREEDOMS II and TRANSFORMS [10-13]. Data from all studies showed that the incidence of infections was similar in patients receiving continuous fingolimod 0.5 mg and patients switching to placebo or Interferon (IFN)  $\beta$ -1a. The safety data from the supportive studies were in line with the safety data from the pivotal clinical studies [10-13]. The integrated analysis showed that there was no overall increase in the risk of infection in patients treated with fingolimod compared to patients treated with placebo. Serious infections occurred in a similar proportion of patients receiving fingolimod 0.5 mg or placebo. *Cryptococcus* can be acquired through inhalation of spores and requires intact cellular immunity to prevent infection and spread. In particular, T-cell mediated immunity is critical in the formation of granulomas of this pathogen and its inhibition [10]. *Cryptococcus neoformans* is the most common cause of fungal meningitis in humans and usually occurs in severely immunocompromised patients [14]. *Cryptococcus* affects people of all ages and is found worldwide. It is the fourth most common infection in Acquired Immunodeficiency Syndrome (AIDS) and also occurs in patients with other forms of immunosuppression. Patients with cryptococcal meningitis show neurological symptoms, most commonly headache and mental disorders, as well as fever, nausea, and vomiting. Without treatment, the disease progresses and symptoms include confusion, seizures, decreased level of consciousness, and eventually coma. CSF analysis typically shows lower cells counts (0-50 cells/ $\mu$ L) in patients diagnosed with Human Immunodeficiency Virus (HIV) than in non-HIV patients (20-200 cells/ $\mu$ L). *Cryptococcus* can be cultured from CSF within 48 to 72 hours. The unspecific



clinical signs and CSF chemistry often delay diagnosis resulting in an increased morbidity and mortality [15]. Published case reports of cryptococcal infections in patients with MS include cryptococcal meningitis causing obstructive hydrocephalus, cutaneous cryptococcosis and cryptococemia, primary cutaneous cryptococcosis, disseminated cryptococcosis, cryptococcal meningoencephalitis, and disseminated cryptococcosis [8,16-23]. In addition, during searching databases and literature, several case reports of cryptococcal meningitis during treatment with fingolimod were found [5,14,16,20-22]. Fingolimod was discontinued in the majority of these patients and they were treated with antifungal drugs [16,19-22]. Guidelines for the use of immunomodulatory therapy in the treatment of RRMS with drugs used to treat opportunistic infections have yet to be established. Diagnostic considerations include serum culture and cryptococcal serology, neuroimaging and, most critically, CSF sampling for microscopy, culture and antigen testing. Antifungal protocols can be extrapolated from regimes used for non-human immunodeficiency virus immunocompromised patients [23]. Discontinuation of any immunomodulatory medication and initiation of antifungal therapy is mandatory for the successful treatment of cryptococcal meningoencephalitis. Induction therapy with amphotericin B in combination with flucytosine (or fluconazole) for at least 2 weeks is recommended [24]. Discontinuation of fingolimod has also led to immune reconstitution inflammatory syndrome, therefore lymphocyte counts should be closely monitored after fingolimod discontinuation. Cryptococcal meningitis has also been reported to occur months after fingolimod cessation [25].

In summary, fever, headache and confusion in combination with fingolimod-induced lymphopenia should always be taken as a warning sign for cryptococcosis and a lumbar puncture is indicated. While only a few such cases have been reported worldwide so far, continued vigilance is needed in MS patients undergoing immunomodulatory therapy, as delayed treatment of cryptococcal meningitis is associated with increased morbidity and mortality. In this report, we describe a case of cryptococcal meningitis susceptible to standard induction therapy. However, at present the patient is without an MS course modulating treatment. This illustrates the treatment problems that arise in MS patients treated with immunomodulatory therapy who develop an opportunistic infection.

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