Cryptococcal Meningoencephalitis Treated with Fingolimod in a Patient with Multiple Sclerosis

Abstract

Cryptococcus neoformans is an opportunistic fungal agent, which may cause infection depending on the state of immunity. The agent is especially prone to be localized in the central nervous system. Fingolimod is an immunomodulatory drug that is used in the treatment of Multiple Sclerosis (MS). The use of this drug leads to a decrease in lymphocyte count and thus might result in the occurrence of the opportunistic infections like Cryptococcosis. In this article, we present a MS patient that underwent fingolimod treatment and developed Cryptococcus meningoencephalitis.

Keywords: Cryptococcus neoformans; fingolimod; multiple sclerosis

Cryptococcus neoformans (C. neoformans), the Cryptococcosis agent that is among the opportunistic systemic fungal infections, is a capsulated fungus that can be isolated from the earth contaminated with pigeon and chicken feces. While it is not found in the human flora, it can colonize without causing disease. The state of immunity is the most important determinant of the process of infection. The agent is commonly transmitted via inhalation, spreads through the blood and is prone to be localized in the central nervous system. Human immunodeficiency virus (HIV), which is almost always CD4<100/mm³, can be encountered in transplantation, hematogenic malignancies, sarcoidosis, chronic renal disorders, diabetes mellitus, cirrhosis and immunodeficient patients under corticosteroid medication.

Fingolimod is an oral immunomodulatory drug used in the recurrent forms of Multiple Sclerosis (MS). In this context; previously, Cryptococcal neoformans meningitis was reported in patients with MS using fingolimod. Fingolimod is a Sphingosine 1 phosphate analogue and decreases the transfer of the auto reactive lymphocytes to the central nervous system by inhibiting the release of the lymphocytes in the peripheral lymph nodes to the periphery via SP1 receptors. Although it is reported that Fingolimod reduces the number of the B-lymphocytes, CD4 and CD8 lymphocytes, the B-lymphocytes and CD4 lymphocytes are affected more profusely. The neuropathological process of MS is facilitated by these effects. The development of the Cryptococcus infection is associated with idiopathic CD4 lymphocytopenia.
CASE REPORT

A 30-year old male patient was admitted with the complaints of sudden headache, diplopia, diagnosed with MS and, following the 3 days of high dose corticosteroid treatment, interferon beta-1a treatment was initiated. The patient did not suffer any exacerbations for two years but due to the complaints of ataxic walk and weakness in left arm and leg, 0.5 mg/day oral fingolimod treatment was started in April 2012 with the diagnosis of MS. There were no complaints or attacks until April 2017 when propranolol treatment was started due to the complaints of headache which was thought to be tension-type headache. However, for the reasons of the exacerbation of the headache that was present for 2 months and night fever, 2 gr/day empirical ceftriaxone treatment was started at the external center by considering community-acquired infection. Patient was on her third day of ceftriaxone when she applied to our university hospital. Ceftriaxone treatment was initiated at the external center after the required investigations were requested. In the 3rd day of the treatment, the patient came to our hospital with the complaint of difficulty in speech. The physical examination of the patient revealed the signs of 39°C body temperature, dysarthric speech, 4/5 muscle strength in the left upper extremity, bilateral clonus more apparent in the left and ataxic walk. In the laboratory examination (complete blood count) the leucocyte number was 5020/UL (80% neutrophil and 6.5% lymphocyte), serum C reactive protein was 1.1 mg/dl and the sedimentation rate was 70 mm/hour. Along with the demyelinating lesions consistent with MS in the contrast cranial and diffusion MR, the signal increases consistent with the ineffective process inside the sulci in both cerebral and cerebellar hemispheres, the hyper-intense signal changes in the FLAIR sequences along the ependymal surfaces and linear contrasts at the level of pre-pontin interpeduncular system were found. There was no contrast demyelinating lesions (Figure 1).

In the cerebrospinal fluid (CSF) obtained by lumbar puncture 110 leucocyte/mm³ (70 lymphocytes), CSF/Serum glucose 4/93 mg/dl, CSF protein 114 mg/dl, CSF chloride 110 mEq/L were detected. There were no bacteria or fungus cells in the CSF. CSF was negative for AARB. Mycobacterium tuberculosis PCR was negative in CSF. The CSF Cryptococcus antigen test was not performed due to lack Cryptococcus antigen scanning kit. The fingolimod treatment was stopped. Pre-diagnosis of meningitis, 12 g/day Ampicillin was added to the ceftriaxone 4gr/day treatment, which had started in an external centre 3 days before the admittance to the hospital. Before, only ceftriaxone was started at the external center.

FIGURE 1: Axial MRI T1 post-contrast image, demonstrating intra-extra parenchymal contrast (A). Coronal MRI T1 post-contrast image, demonstrating intra-extra parenchymal contrast (B).
C. neoformans grew in CSF culture. 350 mg/day liposomal amphotericineB and 800 mg/day fluconazole were started. Ceftriaxone and Ampicillin was discontinued. The lymphocyte count was 620/mm³, CD4 count was 192/mm³, and CD8 cell count was 198/mm³ and the lymphocytopenia was spotted. The CSF oligoclonal band was type3 (+). Fever occurred in the 6th day of the treatment. In the 8th day of the treatment, 10 lymphocyte/mm³ was seen in the CSF microscopy and CSF/serum glukoz 12/88 mg/dl, CSF protein 106 mg/dl were determined. There was no growth in the control CSF fungal culture and in mycobacterium tuberculosis culture. The induction therapy was given for 4 weeks. After oral 800 mg/day Fluconazole was completed to 10 weeks, 10 weeks of 400mg/day oral consolidation therapy was started. The patient was discharged with the plan of oral protective treatment with 200 mg/day Fluconazole for 6 months. All the treatment was performed after the informed consent had been obtained orally.

**DISCUSSION**

C. neoformans commonly affects the central nervous system and the lungs. Cryptococcus infection is associated with a disorder that suppresses the immune system, idiopathic CD4 lymphocytopenia or the usage of specific immune modified agents like alemtuzab, infliximab, etnercept, adalimumab.9,10 While there was no disorder that might cause immunosuppression and immunosuppression-specific clinical and laboratory findings in our case, Cryptococcus meningoencephalitis was detected after 5 years of fingolimod treatment. Similar to the Cryptococcus meningitis and widespread cryptococcus infection that are associated with the fingolimod treatment in literature, CD4 lymphocytopenia was spotted in our case. However, CD4 lymphocytes were not evaluated before the fingolimod treatment. The patients should be controlled in terms of the opportunistic infections by checking the CD4 lymphocyte number before and during fingolimod treatment. While the infections like herpes labialis are encountered commonly during the process of treatment with fingolimod that can be used with ease and success in MS attacks, meningoencephalitis due to the presence of opportunistic pathogens are seen rarely. Chong et al. reported a case of a MS patient on fingolimod therapy with imaging findings, including enhancement pattern and lesion location atypical for active demyelination seen in MS, that were ultimately discovered to be manifestations of cryptococcal meningitis.11 Besides, Ward et al. reported a case of cryptococcal meningitis diagnosed 6 months after fingolimod discontinuation. In this context, MRI findings of that study revealed new intraparenchymal and sulcal contrast enhancement in a basilar predominant distribution, most concerning for an infectious or inflammatory process and again not consistent with demyelinating lesions.12 Furthermore, Achtnichts et al. demonstrated that discontinuation of fingolimod has led to immune reconstitution inflammatory syndrome. An antifungal treatment protocol for human immunodeficiency virus-negative immunocompromised patients has proven to be effective in this setting.13 In the light of this information, our case is the fourth C. neoformans meningoencephalitis associated with the fingolimod usage. The cryptoccus infection generally occurs after 2 years of therapy but it can also occur sooner. The correlation between the treatment time and the infection risk is unknown. The mortality of cryptococcus infection in HIV patients is 30%.14-16 After the patient in our case admitted to the hospital, fingolimod treatment was stopped and clinical healing was achieved by early diagnosis and treatment.

**CONCLUSION**

The patients should be controlled in terms of the opportunistic infections by checking the CD4 lymphocyte number before and during fingolimod treatment. It should be considered that fever, lethargy, lymphocytopenia in case of cognitive disorder or opportunistic infections like cryptococcal infections in case of low CD4 lymphocyte count can be encountered in the MS patients treated with fingolimod.

**Informed Consent**

The patient has given written consent for this case report.
Source of Finance
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Conflict of Interest
No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Murat Terzi; Design: Tuğba Kuruoğlu; Control/Supervision: Tuğba Kuruoğlu; Data Collection and/or Processing: Aydın Deveci, Esra Tanyel; Analysis and/or Interpretation: Tuba Kuruoğlu, Aydın Deveci; Literature Review: Tuba Kuruoğlu; Writing the Article: Tuğba Kuruoğlu; Critical Review: Tuğba Kuruoğlu, Aydın Deveci, Esra Tanyel; References and Fundings: Tuğba Kuruoğlu; Materials: Tuğba Kuruoğlu.

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