Cryptococcal meningo-encephalitis in a fingolimod treated multiple sclerosis patient: unusual presentation underlines the need for vigilance  
  
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Introduction

Fingolimod is an oral sphingosine 1-phosphate (S1P) receptor modulator used in the treatment of active relapsing remitting multiple sclerosis (RRMS). In the UK, it is approved for use as a second line disease modifying therapy (DMT) in adult patients. There are an increasing number of reports of opportunistic infections in the context of immunomodulatory treatment with fingolimod [1].

Case history  
  
We describe the case of a 21-year-old female who presented with cryptococcal meningo-encephalitis in the context of fingolimod treatment for multiple sclerosis (MS). The patient was diagnosed with RRMS at age 13 on a clinico-radiological basis following three characteristic clinical episodes. She was started on natalizumab as first-line therapy but this was not tolerated so after the first few infusions, treatment was switched to fingolimod 0.5mg once daily (OD) five years ago. She had remained stable since with no complications or clinical relapses.  
  
The patient presented to the emergency department (ED) with a one-day history of a sudden onset, severe bi-frontal headache, which woke her up from sleep. There was associated mild photophobia, occasional nausea and general malaise, but there was no history of fevers, neck stiffness, phonophobia, positive visual symptoms, limb weakness or sensory symptoms at initial presentation or at any point throughout the clinical course. The patient had travelled around Europe extensively over the preceding few years. Examination in the emergency department was unremarkable. In particular, there was no nuchal rigidity or rash, and a full neurological examination was normal. Her vital signs showed a mild tachycardia and no pyrexia. Initial investigations showed: WCC 7.3, lymphocytes 0.53, CRP 19, normal lactate, normal renal and liver function, sinus tachycardia on ECG, an unremarkable CT head (no evidence of intracranial or subarachnoid blood) and a normal CT venogram.  
  
A lumbar puncture was performed primarily to rule out subarachnoid haemorrhage. The opening pressure was 33 cm H20, and CSF constituents: WCC < 5, RBC 1360, protein 0.94g/L, and no evidence of bilirubin or oxyhaemoglobin on spectrophotometry. CSF MC&S showed a light growth of Cryptococcus neoformans, which was subsequently confirmed on India Ink staining as well as by a strongly positive Cryptococcus antigen test titre of 1:100. These findings prompted a further screen for immunodeficiency: HIV serology was negative (on two occasions) as was HTLV-1. T cell subsets showed suppressed absolute counts of CD3, CD4, CD8, CD19 and CD56 cells (see table 5 in appendix) as would be expected with fingolimod. Magnetic resonance imaging showed old pre-existing MS lesions only.  
  
The diagnosis of cryptococcal meningo-encephalitis in the context of fingolimod was made. Following discussion with microbiology and infectious disease physicians, the patient was commenced on anti-fungal induction therapy consisting of intravenous amphotericin (3mg/kg) OD and intravenous flucytosine 1500mg QDS for two weeks. This was followed by high dose oral fluconazole 800mg OD for 8 weeks, and a maintenance dose thereafter.   
  
Following lumbar puncture and induction therapy the patient made an excellent recovery. Her headache and photophobia gradually resolved over a period of two weeks. Subsequent lumbar punctures showed a gradual reduction in opening pressure, though the cryptococcal antigen remained positive on the second and third lumbar punctures (see table 3 in appendix).  
  
Fingolimod was stopped on the day of the first lumbar puncture results. After allowing a few months for recovery the patient was started on ocrelizumab.   
  
Discussion

To our knowledge this is the 15th case in the literature of cryptococcal meningo-encephalitis in a MS patient treated with fingolimod. We compared the clinical characteristics of the 15 published cases in the literature (table 1).

The heterogeneity in clinical symptoms at presentation and laboratory investigations across these 15 cases is striking. Of all the clinical symptoms at initial presentation, the two that were most common were headache (13/15; 87%) and confusion (6/15; 40%). Our case was unique in the type of headache presentation, with a sudden onset severe headache not being described before, leading to an initial working diagnosis of subarachnoid haemorrhage. Aside from CSF cryptococcal antigen none of the serum or CSF markers were invariably abnormal in these 15 cases. CSF pleocytosis was seen in the majority of cases (12/14; 86%) though there was a wide range of absolute white cell counts. There were two cases, including our case, with CSF WCC < 5, which highlights the important point that CNS cryptococcal infection in the setting of immunosuppression can occur despite a normal CSF cell count. Raised CSF opening pressures were also seen in most cases (7/10; 70%). Most of the reported cases (9/13; 69%) presented in the context of grade 3 or grade 4 lymphopenia.

The mortality rate seen in these 15 cases (2/15; 13%) was roughly in line with that seen in CNS cryptococcal infections in general. This seems to suggest that developing a CNS cryptococcal infection in the context of fingolimod does not confer any additional risk of mortality as would otherwise be expected. Three patients out of 15 (20%) developed immune reconstitution inflammatory syndrome following fingolimod cessation.

Our patient’s fingolimod was stopped when she was diagnosed with cryptococcal meningo-encephalitis. It was felt that fingolimod should not be restarted in the future, not for lack of efficacy but rather because of the risk of recurrence of invasive fungal infection, especially in view of the known association with fingolimod (table 1). Fingolimod is also associated with other infections (summarised in table 2).

The decision regarding which alternative disease modifying treatment to use is always a difficult one. At the time, the national Blueteq High Cost Drugs prescribing system in the UK would have allowed for a switch to a platform treatment (with lower efficacy than fingolimod, so a de-escalation) or ocrelizumab (representing an escalation). Since then, ofatumumab and ponesomid have also become available. When switching from fingolimod, the duration of the washout interval needs to consider the risk of rebound of MS activity [2] so that commencement of the alternative disease modifying treatment may need to occur before full immune reconstitution, usually within days or weeks, and certainly under one month [3]. In our case it was also important to balance this with the need to allow sufficient time for recovery from a serious CNS infection. The decision was made to switch to ocrelizumab, since the alternatives would have represented a de-escalation, and there have been no case reports, or descriptions in clinical or observational studies, of cryptococcal meningitis in MS patients treated with anti-CD20 monotherapy. The only cases of cryptococcal meningitis reported so far occurred in two non-MS patients, in the context of rituximab use alongside other immunosuppressants [4] and in an already immunocompromised patient [5].

As the MS DMT landscape continues to expand, including treatment on the progressive subtypes of the condition, this case is a reminder of the importance of pharmacovigilance. One must balance the efficacy of newer immunosuppressive agents with their potential complications. Although CNS cryptococcal infection in the context of fingolimod for MS remains very rare, it is associated with significant morbidity and mortality and thus a high degree of suspicion should be maintained. It is not infrequent that people with MS on disease modifying treatment may 'forget' to mention it as part of a drug history, especially in the case of infrequent infusions, or perhaps because DMTs are often dispensed via tertiary care and may not be part of their routine medical history. Some may also be unaware of, or have forgotten, the potential link of their MS treatment with infection risks, so it is always good practice to remind people of this risk during follow-up appointments.

Key points

* CNS infection can sometimes present with sudden onset severe headache without any other associated clinical features - mimicking subarachnoid haemorrhage.
* Patients presenting with cryptococcal meningo-encephalitis in the context of fingolimod can have completely normal CSF white cell counts. This can be falsely reassuring and cryptococcal tests should still be performed.
* Atypical presentations are more likely in immunosuppressed patients so a high degree of suspicion must be maintained when treating these patients.
* Certain immunomodulatory treatments can predispose patients to specific infections, therefore taking a thorough medication history is always good clinical practice.
* Reminding patients of the risk of atypical infections with immunosuppressive treatments during follow-up appointments is advised.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Report | Clinical features | Fingolimod duration (years) | Serum lymph (x109) | CSF  OP | CSF WCC | Serum culture | CSF MCS | Serum CrAg | CSF CrAg | MRI | Outcome |
| This case | Sudden onset severe headache | 5 | 0.53 | 33 | < 5 | - | + | ND | 1:100 | Old MS lesions only | Good |
| Aoki et al, 2021 [6] | Headache; fever; neck stiffness | 6 | 0.17 | ND | 65 | ND | + (II) | 1:2048 | 1:256 | LM enhancement | ND |
| Cuascut et al, 2021 [7] | Severe headache; confusion; seizures; nausea; photophobia; phonophobia; inattention | 7.6 | 0.21 | > 55 | 99 | ND | + | ND | 1:1024 | LM enhancement parietal region; old MS lesions | Good;  IRIS |
| Kaur et al, 2021 [8] | Headache; ataxia; constitutional upset | 5 | ND | 48 | 8 | + | + | >1:2560 | ND | Old MS lesions only | ND |
| Baghbanian et al, 2021 [9] | Headache; blurred vision; confusion; meningism; ataxia | 5 | 0.25 | 25 | 20 | ND | + | ND | + | Right enhancing occipital lesion; LM enhancement | Good; VP shunt; |
| Ma et al, 2020 [10] | Headache; fever; confusion | 7 | 0.9 | 29 | 62 | ND | + | 1:2560 | 1:5120 | Cerebritis of both parietal lobes;  LM enhancement | Good |
| Wienemann, 2020 [11] | Headache; fever; confusion; malaise | 5.5 | 0.09 | Normal | 54 | + | -  (then +) | ND | 1:160 | Old MS lesions only | Good |
| Chong et al, 2019 [12] | Headaches; anorexia; hallucinations | 2.25 | 0.2 | Normal | 22 | + | + | + | + | Enhancing lesions; LM enhancement | Good |
| Anene-Maidoh et al, 2018 [13] | Headache; seizures; confusion; ataxia | 4.75 | ND | 50 | 48 | ND | + | + | + | Multiple infarcts;  raised ICP | Death |
| Pham et al, 2017 [14] | Headache; neck pain; nausea; vertigo; anorexia | 3 | 0.12 | ND | ND | - | - | + | + | Obs. hydro.; nodular LM enhancement; 4th ventricle compression | Good; required ventriculostomy |
| Ward et al, 2016 [15] | Dysarthria; dysphonia; vomiting; confusion; cognitive changes; right INO | 4.33 | 2.4 | ND | 240 | ND | + | + | 1:40 | Intraparenchymal hyperintensity with contrast enhancement; multiple acute infarcts; | IRIS;  death |
| Seto et al, 2016 [16] | Multiple cutaneous lesions (positive tissue culture); asymptomatic lung lesions; UMN facial palsy; gaze palsy; dysarthria; ideomotor apraxia | 2 | 0.3 | 16 | 74 | - | - | 1:256 | 1:1040 | Old MS lesions only | Reduced function but survived |
| Grebenciucova et al, 2016 [17] | Headache; confusion; dizziness | 2.75 | 0.34 | ND | 203 | ND | + (II) | ND | + | Old MS lesions only | Good |
| Huang et al, 2015 [18] | Disseminated cryptococcal infection with CNS involvement; headaches initially; then nausea, ataxia and drowsiness | 3.5 | 0.5 | ND | 3060 (?) | + | + | 1:128 | 1:108 | Ring enhancing hyperintense lesions (abscesses) and areas of LM enhancement | Good |
| Achtnichts et al, 2015 [19] | Bilateral headache; photophobia; dysarthria; ataxia | 2 | 0.4 | 9, 38 | 3, 20 | ND | + | + | 1:2048 | Non-enhancing WM lesions; new lesions a few weeks later | Good;  IRIS |

Table 1: comparison of clinical features and parameters of all published case reports of CNS cryptococcal infection in fingolimod treated MS patients; OP = opening pressure; WCC = white cell count; II = India Ink; CrAg = cryptococcal antigen; LM = leptomeningeal; IRIS = immune reconstitution inflammatory syndrome; WM = white matter; ICP = intracranial pressure; VP = ventriculoperitoneal; + = positive; - = negative; ND = no data

|  |  |
| --- | --- |
| **Infections associated with fingolimod** | **References** |
| Influenza | [20] |
| Cryptococcus | [6-19] |
| Pneumonia | [20] |
| JC virus related progressive multifocal leukoencephalopathy | [21] |
| Herpesviruses | [20] |
| Human papilloma virus | [22] |
| Listeria | [23] |
| Tinea versicolor | [24] |

Table 2: infections that have been associated with fingolimod use

Appendix

|  |  |  |  |
| --- | --- | --- | --- |
| Lumbar puncture no. | Day 2 | Day 8 | Day 17 |
| Opening pressure (cm H2O) | 33 | 27 | 21 |
| Closing pressure (cm H2O) | Not done | Not done | 15.5 |
| WCC (x 10\*6/L) | < 5 | < 5 | 41 (100% lymphocytes) |
| RBC (x 10\*6/L) | 1360 | < 5 | < 5 |
| Protein (g/L) | 0.94 | Not done | Not done |
| CSF glucose (paired serum) | 3.0 (not done) | Not done | Not done |
| MCS | Light growth cryptococcus neoformans | No organisms seen No growth on culture | No organisms seen No growth on culture |
| India Ink | Positive | Negative | Negative |
| Cryptococcal antigen | 1:100 | 1:100 | 1:100 |
| Xanthochromia | Negative |  |  |

Table 3: serial CSF results

|  |  |
| --- | --- |
| HIV | Negative |
| HTLV | Negative |
| Toxoplasma screen | Negative |
| CMV IgM | Negative |
| SARS-CoV-2 RNA | Not detected |
| HBsAg | Not detected |
| HCV IgG | Not detected |

Table 4: other relevant results

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Blood results | Day 1 | Day 4 | Day 6 | Day 15 | Day 22 | Normal range |
| WCC ( x 109/L) | 7.3 |  | 6.3 |  | 7 | 4 - 11 |
| Neutrophils ( x 109/L) | 6.2 |  | 5.2 |  | 5.4 | 2 – 7.5 |
| Lymphocytes ( x 109/L) | 0.53 | 0.21 | 0.28 |  | 0.75 | 1 – 4 |
| CRP (mg/L) | 19 |  | 21 |  | 12 | 0 - 10 |
| CD3 ( x 106/L) |  |  | 241 | 416 |  | 918 – 2023 |
| CD4 ( x 106/L) |  |  | 6 | 61 |  | 455 – 1320 |
| CD8 ( x 106/L) |  |  | 113 | 209 |  | 140 – 906 |
| CD19 ( x 106/L) |  |  | 5 |  |  | 42 – 461 |
| CD56 ( x 106/L) |  |  | 74 |  |  | 90 – 600 |

Table 5: serial haematology results

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