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SM Journal of Neurology and Neuroscience

Case Report

Meningoencephalitis in a Lymphopenic Dimethylfumarate Treated Multiple Sclerosis Patient

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Article Information

Received date: Mar 16, 2018
Accepted date: Apr 18, 2018
Published date: Apr 20, 2018

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Abstract

Short summary: We report an incidence of bacterial meningoencephalitis with an otherwise low-virulent infectious agent, following monotherapy with dimethylfumarate (DMF) in an elderly woman with Relapsing Remitting Multiple Sclerosis (RRMS). DMF was first lowered to half the dose and eventually discontinued due to persistent lymphopenia.

A well known side effect of DMF is lymphopenia. In elderly patients DMF induced lymphopenia may provoke severe infection with otherwise ubiquitous low-virulent agents. We recommend caution when prescribing DMF to elderly RRMS patients in case of lymphopenia and discontinuation may need to be considered even at mild-moderate lymphopenia in elderly RRMS patients.

Background

DMF is recommendedas a first-tier treatment in patients with RRMS. Since the implementation of DMF in RRMS, five cases of Progressive Multifocal Leukoencephalopathy (PML) have been reported in DMF treated MS. None of these patients had previously received immunomodulatory therapy. According to EMA guidelines treatment with DMF should be discontinued in severe lymphopenia when lymphocyte count drops below $0.5x10^9$/L [1]. DMF may be administered to other patients with autoimmune disease, such as psoriasis (Fumaderm) and ongoing clinical trials study its effect in patients with T cell lymphoma the exact mode of action of DMF is not clear, however, experimental data highlight its role in inhibiting the NF-κβ signalling pathway leading to T cell apoptosis in subsets of T cells [2].

Case Presentation

We report a 65 year-old woman diagnosed with RRMS in 1995 presenting with aleft optic neuritis followed by a right optic neuritis in 2003. Her last clinical attack was reported in 2009 with a left leg paresis. From time of diagnosis to admission in our department she demonstrated only a slight progression in EDSS from initially 3 to 4. Follow-up brain MRI, however, was suggestive of possible radiographic disease activity and the patient was switched from glatiramer acetate treatment to DMF in 2014. Clinically, she presented with visual impairment and she was able to swim, walk 5 kilometres and required no assistance in walking or activities of daily living.Co-morbidities included hypertension, diabetes mellitus, glaucoma and a previous occipital stroke.

Lymphocyte blood counts were performed prior to initiation of DMF and were all within normal range (baseline white blood cells $7,3x10^9$/L, lymphocytes $2,1x10^9$/L). After 6 months of treatment she developed protracted lymphopenia with counts dropping to $0.7x10^9$/L which further decreased to $0.5x10^9$/L at 9 month follow-up. DMF dose was lowered to half the dose. In spite of this, lymphopenia dropped to $0.36x10^9$/L and DMF was discontinued after 18 months of treatment.

One month after cessation of DMF the patient was still lymphopenic and admitted to our department in prolonged status epilepticus. Neurological exam demonstrated near blindness, slurred speech, confusional state and decreased level of consciousness. Moreover, she had a fever (39.2^0 C). A brain CT scan was without any acute changes. Blood counts revealed leucocytes of $14.1x10^9$/L and lymphocytes of $0.30x10^9$/L. Lumbar puncture demonstrated severe polymorphic leucocytosis with $584x10^6$ cells/L. Treatment for bacterial meningoencephalitis concurrent with acyclovir was initiated. A control MRI was performed and demonstrated acute hyperintense changes in the left insula, thalamus and hippocampus consistent with encephalitic changes. Despite prompt microbial therapy, the patient developed respiratory failure and was admitted to the ICU for 3 weeks. Continued EEG monitoring revealed paroxysmal focal activity from the left occipito-

parieto-temporal region. Extensive infectious work-up including JC virus were all negative except from a positive 16S rRNAPCR for Chryseobacterium in the spinal fluid. The patient was discharged from the hospital no longer able tocare for herself independently and was subsequently readmitted four times with prolonged status epilepticus prior to final dismission to a nursing home.

Discussion

Chryseobacterium is a ubiquitous bacterium found in soil and plants and has been associated with meningoencephalitis in immunocompromised adults [3,4]. In a study by AH Cross et al., [5] of 144DMF treated patients 14% of the patients developed grade 2 or 3 lymphopenia. The risk of severe lymphopenia was significantly higher at ≥55 years of age. Despite normal baseline lymphocyte count, no prior treatment with natalizumab or concurrent treatment with immunosuppressive or immunomodulatory drugs, our patient developed severe prolonged lymphopenia and subsequently meningoencephalitis not related to JC virus. It remains plausible that the severe lymphopenia secondary to DMF treatment rendered the patient susceptible to meningoencephalitis by an otherwise low pathogenic environmental agent, chryseobacterium. Moreover, higher age could be a possible risk factor of lymphopenia in DMF treatment, which may be associated with an increased risk of opportunistic infections.

Conclusions

Current EMA guidelines and national guidelines recommend discontinuation of DMF when lymphocyte count drops below $0.5x10^9$/L. Since the occurrence of a fifth case of PML in DMF treated MS patients, updated guidelines recommends risk-benefit stratification in DMF associated lymphopenia. Serial measurements revealing continuous lymphocyte counts between $0.8x10^9$/L-$0.5x10^9$/L should prompt consideration of testing JC virus seropositivity. This case report highlight the need for risk-benefit stratification in patients ≥55 years of age, even in patients with normal baseline lymphocyte counts. When elderly patients develop lymphopenia due to DMF we suggest considering discontinuation rather than lowering the dose. This case report, to the best of our knowledge, is the first report of severe meningoencephalitis due to chryseobacterium in an adult MS patient treated with DMF. This case report further highlights that DMF induced lymphopenia mimics an immunocompromised state, especially in elderly MS patients, which may increase the risk of serious brain infections completely unrelated to JC virus status.

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