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LETTER TO THE EDITORS

Legionella infection associated with dimethyl fumarate used for treatment of multiple sclerosis

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Dear Sirs,

Multiple sclerosis (MS) causes demyelination in the central nervous system. Treatment is often immunomodulation, which puts patients at risk of developing infections [1].

Dimethyl fumarate (DMF) is a disease-modifying therapy approved in 2013 for treatment of relapsing–remitting MS. It is hypothesized to activate the nuclear factor (erythroid-derived-2)-like 2 (Nrf2-ERK1/2) and mitogen-activated protein kinase (MAPK) pathways [2, 3]. These promote expression of products that protect against oxidative stress, which can inhibit proliferation of lymphocytes and hematopoietic stem cells [2, 3]. DMF has been shown to decrease mean lymphocyte counts by 30% in the first year of use [3].

Legionella pneumophila is a Gram-negative organism that can cause pneumonia with a mortality rate of 10% [4]. It is found in water and soil, and risk factors for infection include age, smoking, contaminated water exposure, and being immunocompromised [4].

This case describes a lymphopenic patient taking DMF who developed severe Legionella pneumonia.

A 50-year-old immunocompetent patient with relapsing–remitting MS diagnosed in 2009, obstructive sleep apnea with occasional CPAP use, and tobacco use on DMF presented with 4 days of fever, malaise, and cough. He started DMF 2 years prior to admission with a normal baseline white blood cell count differential but had no further monitoring during therapy. Patient had been stable on DMF and had not had any MS flares while taking it. He had no limitations in functional activity. Prior to being on DMF, he had tried glatiramer acetate. On admission to the hospital, he was febrile, tachycardic, and hypoxic with a leukocytosis and lymphopenia. His absolute lymphocyte count (ALC) was 300 cells/mm^3. Chest X-ray showed a right perihilar and lower lobe consolidation and he had proteinuria, hematuria, and hyponatremia. The patient was admitted to the hospital and intubated for hypoxic respiratory distress. Levofloxacin and cefepime were started for broad-spectrum coverage of community-acquired pneumonia. Urine legionella antigen was positive and treatment was narrowed to levofloxacin 750 mg daily for 14 days. The patient gradually improved. DMF was held during admission. Direct fluorescent antibody for legionella (DFA) was negative.

Although anti-(TNF)-α and anti-CD52 therapy are known risk factors for Legionella infection, this appears to be only the second reported case of severe Legionella pneumonia in a patient receiving DMF [5]. Our patient's DFA was negative, however, this test has a sensitivity of 25–85% [6]. Given the clinical course and positive antigen, the DFA was considered a false negative.

In Legionella infection, cellular immune response is more important than humoral response in host defense. Cytokines produced by infected alveolar macrophages recruit neutrophils which stimulate an immune response [2]. Patients with lymphopenia and decreased cellular immunity are more susceptible to Legionella infection [2].

In MS clinical trials, the incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with DMF or placebo [7]. However, progressive multifocal leukoencephalopathy (PML), a potentially fatal disease of the central nervous system, has been reported in 21 patients receiving DMF, 5 of whom were MS patients [8]. The majority of cases occurred in patients with lymphocyte counts $< 0.5 \times 109$/L [7, 9]. As a consequence, the DMF prescribing information recommends monitoring a complete blood cell count (CBC) at initiation, after 6 months, and every 6–12 months, although newer guidelines recommend monitoring every 3 months [10]. There are currently no other infection warnings on the drug packaging [11].

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Clinicians should be aware of the potential increased risk of Legionella infection with DMF. It is unknown whether a lower dose of DMF decreases the incidence of lymphocytopenia. However, lower doses have not demonstrated a significant effect on MRI endpoints of MS activity compared with placebo [12].

We recommend clinicians monitor a complete blood cell count with differential every 3 months for patients on DMF and have an increased awareness of the risk of Legionella infection.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standards This article does not contain any studies involving human participants performed by any of the authors.

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