

Acute exacerbation of Hashimoto's thyroiditis in a patient treated with dimethyl fumarate for multiple sclerosis

A case report

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Abstract

Introduction: Dimethyl fumarate (DMF) has been recently approved for first-line monotherapy of Multiple Sclerosis (MS). Its effects are due to mechanism modulating the immune system and activating antioxidative and neuroprotective pathways.

Patient concerns: A 59-year-old female patient affected by chronic Hashimoto's thyroiditis (HT) from 10 years was diagnosed with relapsing remitting MS in 2013. She started therapy with DMF in November 2016.

Diagnosis: After 2 months of therapy with DMF, the results of thyroid function test were abnormal. Thyroid ultrasonography confirmed the diagnosis of acute exacerbation of HT.

Interventions: This condition led to discontinuation of DMF therapy.

Outcome: Two months after the interruption of DMF therapy, the findings of thyroid function test were within normal limits.

Conclusion: The association of MS with autoimmune thyroid diseases supports a common immune-mediated pathogenic mechanism. We assume that the acute exacerbation of HT in our MS patient is associated not with the immunomodulatory effect of DMF but rather with its antioxidative mechanism.

Constant monitoring of thyroid hormone levels should be recommended especially if the MS patients in treatment with DMF are affected by concomitant autoimmune thyroid diseases.

Abbreviations: ATDs = autoimmune thyroid diseases, BBB = blood brain barrier, CNS = central nervous system, DMF = dimethyl fumarate, GSH = reduced glutathione, HT = Hashimoto's thyroiditis, ICAM-1 = intercellular adhesion molecule 1, IFN- β = interferon- β , IL-4 = interleukin-4, MMF = monomethyl fumarate, MS = multiple sclerosis, NO = nitric oxide, Nrf2 = nuclear erythroid 2-related factor 2, PML = progressive multifocal leukoencephalopathy, RR = relapsing-remitting, Th1 = helper T1, Th2 = helper T2, TNF- α = tumour-necrosis factor A, TSH = thyroid-stimulating hormone, VCAM-1 = vascular cellular adhesion molecule 1.

Keywords: Adverse event, autoimmune thyroid diseases, case report, dimethyl fumarate, Hashimoto's thyroiditis, multiple sclerosis

1. Introduction

Multiple sclerosis (MS) is a complex immune-mediated disease of the central nervous system (CNS) characterized by inflammation,

demyelination, and axonal degeneration. The complex inflammatory etiology of MS involves cells of innate and adaptive immune systems. In early stage of MS, the neuro degeneration is induced by inflammation; later in the course of the disease, other factors may contribute to neural damage, as oxidative stress.

Dimethyl fumarate (DMF-Tecfidera) is an oral agent that is hydrolyzed to its primary metabolite, monomethyl fumarate (MMF). DMF has been used for long time to treat psoriasis. It has been recently approved as a disease-modifying therapy (DMT) for treatment of relapsing-remitting (RR) MS.

Although the exact mode of action by which DMF and MMF exert their effects in MS is still unclear, it is thought they have dual mechanism: modulating the immune system and activating antioxidative and neuroprotective pathways.^[1] The immunomodulatory effects include (i) induction of a shift from helper T1 (Th1) (proinflammatory) to Th2 (anti-inflammatory) cytokine response, with the increase of interleukin-4 (IL-4), IL-5 and IL-10 production, and the decrease of IL-6, IL-1 β and tumor-necrosis factor α (TNF- α) expression; (ii) downregulation of intracellular adhesive molecules, such as intercellular adhesion molecule 1 (ICAM-1) and vascular cellular adhesion molecule 1 (VCAM-1) expression, which is supposed to reduce lymphocyte migration

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across the blood brain barrier (BBB); (iii) suppression of nitric oxide (NO) synthesis in microglia and astrocytes. DMF and MMF exert antioxidative and neuroprotective effects by activating the nuclear erythroid 2-related factor 2 (Nrf2) transcriptional pathway, which plays a central role in oxidative and metabolic stress response, protection of the BBB, and regulation myelin maintenance in the CNS.

Phase II and III clinical trials demonstrated that DMF was effective in improving clinical and radiological disease activity; in addition, it showed good safety and tolerability profile. The adverse events most commonly reported were flushing and gastrointestinal events, such as diarrhea, nausea, and abdominal pain. Lymphopenia and leukopenia have been significantly associated with DMF.^[2] Furthermore, few cases of progressive multifocal leukoencephalopathy (PML) have been observed.^[3]

In this report, we describe a case of acute exacerbation of Hashimoto's thyroiditis (HT) in an MS patient during the treatment with DMF and its possible pathogenic role.

2. Case

A 59-year-old female patient affected by chronic HT from 10 years was admitted to our MS Center in January 2013 because of paresthesia and motor deficit at the lower limbs. In the same year, she was diagnosed with RRMS according to the McDonald 2010 criteria. She started therapy with DMF in November 2016. She was previously treated for 3 years with interferon- β (IFN- β) 1b 22 μ g subcutaneously 3 times a week from which she was switched to DMF due to flu-like syndrome side effects. In the year before DMF treatment, the patient was clinically and radiologically stable.

During treatment with IFN- β 1b as well as before beginning treatment with DMF, findings of thyroid function test were within normal limits, with positive antithyroid antibodies (Table 1). After 2 months of therapy with DMF, blood-cell count and biochemistry laboratory findings were within normal limits, but not the results of thyroid function test (Table 1). Thyroid ultrasonography, performed in January 2017, confirmed the diagnosis of acute exacerbation of HT. During the treatment with DMF, the patient did not take any other drug excluding l-thyroxine at a daily dose of 75 μ g for HT. DMF therapy was immediately discontinued. Two months after the interruption of DMF therapy, thyroid-stimulating hormone (TSH) was again within normal limits and T3 increased to value more near to normal range (Table 1). We attributed the cause of acute exacerbation of HT to DMF therapy. The patient gave written informed consent to report her case.

Table 1
Thyroid function of MS patient before, during and after DMT therapy.

	TSH (μ UI/mL)	T3 (pg/mL)	T4 (ng/dL)
Normal range	0.30–4.20	2.99–4.40	0.54–1.18
Date			
Before the DMT start (November 2016)	1.76	3.01	1.09
After 2 months of DMF therapy (January 2017)	8.36 \uparrow	2.72 \downarrow	0.74
After 2 months of DMT discontinuation (March 2017)	0.70	2.76 \downarrow	0.94

\uparrow Increased; \downarrow decreased.

3. Discussion

It has been reported an association between MS and autoimmune thyroid diseases (ATDs), such as HT, with a variability from 4% to 22%,^[4] which may support common genetic or environmental exposures. HT is considered the most common autoimmune disease and cause of primary hypothyroidism. A possible pathogenic mechanism of HT is based on assumption that environmental factors in genetically susceptible individuals are responsible for lymphocytic infiltration of thyroid gland, production of thyroid-specific autoantibodies, and progressive destruction of the organ. It is likely that immune and thyroid cells produce proinflammatory cytokines, resulting in predominantly Th1 and Th17 responses with an increased Th1/Th2 ratio, resulting in thyrocyte apoptosis and thyroid destruction.^[5] In addition, HD is linked with the oxidative stress.^[6]

Some DMTs used for MS treatment may raise the risk of autoimmune diseases such as thyroid disease. The development of ATDs has been reported with the monoclonal antibody Alemtuzumab with a frequency of 20% to 33%.^[7] Alemtuzumab leads to significant depletion of all circulating lymphocytes by targeting CD52 antigen present on their surface. The development of thyroid diseases after Alemtuzumab treatment may be associated with faster recovery CD8⁺ T cells that are involved in the pathogenesis of thyroid autoimmunity.

ATDs have been reported also in MS patients receiving IFN- β with a prevalence from 0 to 34%.^[8] IFN- β stimulates the secretion of CXCL10 by human thyrocytes, a prototype Th-1 chemokine that was demonstrated to play a pathogenic role in both MS and ATDs.^[9]

To the best of our knowledge, this is the first case of acute exacerbation of HT associated with DMF therapy. On the contrary IFN- β , the significant DMF-induced reduction of CXCL10, showed in murine and human astrocytes,^[10] does not support the development of HT in our MS patient. However, it has been hypothesized that DMF could cause a brief period of oxidative stress at the beginning of the treatment. Indeed, it seem that DMT activates Nrf2 transcriptional pathway of cell defense as result of an initial depletion of reduced glutathione (GSH).^[11] It has been recently reported that the reduction in GSH status may lead to oxidative stress activation and the development of immunological intolerance in HT.^[12]

Therefore, it is possible that the acute exacerbation of HT in our MS patient is the result not of immunomodulatory effects of DMF but rather of its antioxidative mechanism, in which oxidative stress is initially involved.

Since some symptoms of thyroid dysfunction may overlap with typical MS-related symptoms, thyroid hormone levels should be checked in MS patients treated not only with Alemtuzumab and IFN- β but also with DMF. Constant monitoring of thyroid hormone levels should be recommended especially if the MS patients, treated with DMF, are also affected by concomitant ATDs.

Author contributions

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