DISSEMINATED ZOSTER WITH PARESIS IN A MULTIPLE SCLEROSIS PATIENT TREATED WITH DIMETHYL FUMARATE

Varicella-zoster virus (VZV) reactivation can occur in both immunocompetent and immunocompromised individuals and lead to a range of neurologic manifestations.1 VZV reactivation was recently reported in a man with psoriasis being treated with dimethyl fumarate (DMF).2 Here we describe a woman with relapsing-remitting multiple sclerosis (RRMS) who developed disseminated VZV while receiving delayed-release DMF.

**Case report.** A 40-year-old woman with RRMS presented with pain and new weakness in her right leg 6 months after starting DMF. She was diagnosed with MS in 2005 and treated with several disease-modifying therapies (DMTs), including interferon and natalizumab, followed by 1 cycle of rituximab because of positive JC virus antibody status. She had no history of viral reactivation or opportunistic infections (OIs) and had not had immunotherapy for more than a year before commencing DMF. Moreover, B cell counts repopulated before DMF was initiated. Pre-DMF absolute lymphocyte count (ALC) was 1.8 \( \times 10^9/L \) (CD8 525, CD4 1020). She did not experience an MS relapse or receive steroids while on DMF.

Two weeks prior to presentation, she developed severe shooting pain in her torso and right leg. Subsequently she developed right leg weakness, causing difficulty transferring and walking. On the day of presentation, she developed a rash on the right lower abdomen. Examination revealed vesicular lesions in the right T11-T12 distribution, new right leg weakness, and hyperreflexia. Repeat ALC was 0.7 \( \times 10^9/L \) (CD8 134, CD4 438). 3T brain and spine MRI demonstrated no new/enhancing lesions; DMF was discontinued and she was discharged with oral valacyclovir.

Her leg weakness continued to worsen, prompting admission the following day. Repeat examination demonstrated extension of her rash within the same dermatomes and increased right hip flexor weakness. She was started on IV acyclovir 10 mg/kg every 8 hours. Given her new hyperreflexia, she was treated with 5 days of prednisone (1 mg/kg daily) because of concern for CNS VZV vasculopathy. Repeat imaging 2 days later was unchanged. Her rash progressed to involve the right T10-L1 (figure) and left T6 dermatomes and zoster sine herpete on right T4. On day 4 of symptoms, skin scraping confirmed VZV; CSF was unremarkable (white blood cell count 0, red blood cell count 99, glucose 65, protein 15) and negative for VZV PCR and IgG as well as Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and Lyme disease. Ophthalmology evaluation demonstrated no retinal necrosis or vasculitis, and magnetic resonance angiogram/CT angiogram was normal. Her weakness improved near her baseline within a few days of treatment. Despite her zoster rash resolving over the following weeks, prominent dermatomal neuralgia persisted.

**Discussion.** VZV reactivation has been associated with various MS DMTs. We report a case of DMF-related disseminated herpes zoster in MS.

The DEFINE and CONFIRM clinical trials3,4 demonstrated no increase in the incidence of infections in those treated with DMF compared to those treated with placebo. The incidence of herpes zoster was comparable between the 2 groups, with no report of disseminated herpes zoster. However, the risk of VZV reactivation increases with age because of a decline in cell-mediated immunity, and DMF has been associated with an approximately 30% decrease in lymphocyte counts in the first year of treatment.3,4

Our patient initiated treatment with DMF 6 months prior to presentation, with a subsequent 60% decrease in her ALC compared to baseline. Given the presence of both sensory and motor symptoms as well as a multidermatomal rash, we diagnosed her with disseminated zoster. CSF VZV-IgG is a more sensitive marker than VZV PCR for disseminated VZV; however, because these studies were performed on day 4 of treatment, the sensitivity may have been reduced. She refused EMG for further evaluation because she had robust improvement in her deficits with treatment.

The exact mechanism(s) of action of DMF is unknown, especially as it relates to the emergence of OIs. DMF may preferentially reduce CD8+ T lymphocytes over CD4+ T lymphocytes,6 which could increase an individual’s susceptibility to viral
Several cases of progressive multifocal leukoencephalopathy (PML) have recently been described in the setting of DMF, with 4 cases involving extended-release DMF. Our patient had a 74% decrease in CD8+ T lymphocytes vs a 57% decrease in CD4+ T lymphocytes. DMF-induced lymphopenia likely contributed to VZV reactivation with resultant disseminated zoster. Her prior treatment with rituximab may have also increased her risk of viral reactivation.

DMF’s safety profile is still evolving. With the recent associations of DMF with PML and now VZV reactivation, we recommend more frequent laboratory monitoring and increased suspicion for OIs in patients with lymphopenia. Moreover, as with fingolimod, establishing VZV immune status and vaccinating naïve patients could be considered prior to initiating DMF therapy.

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Disseminated zoster with paresis in a multiple sclerosis patient treated with dimethyl fumarate

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