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PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY DURING FUMARATE MONOTHERAPY OF PSORIASIS

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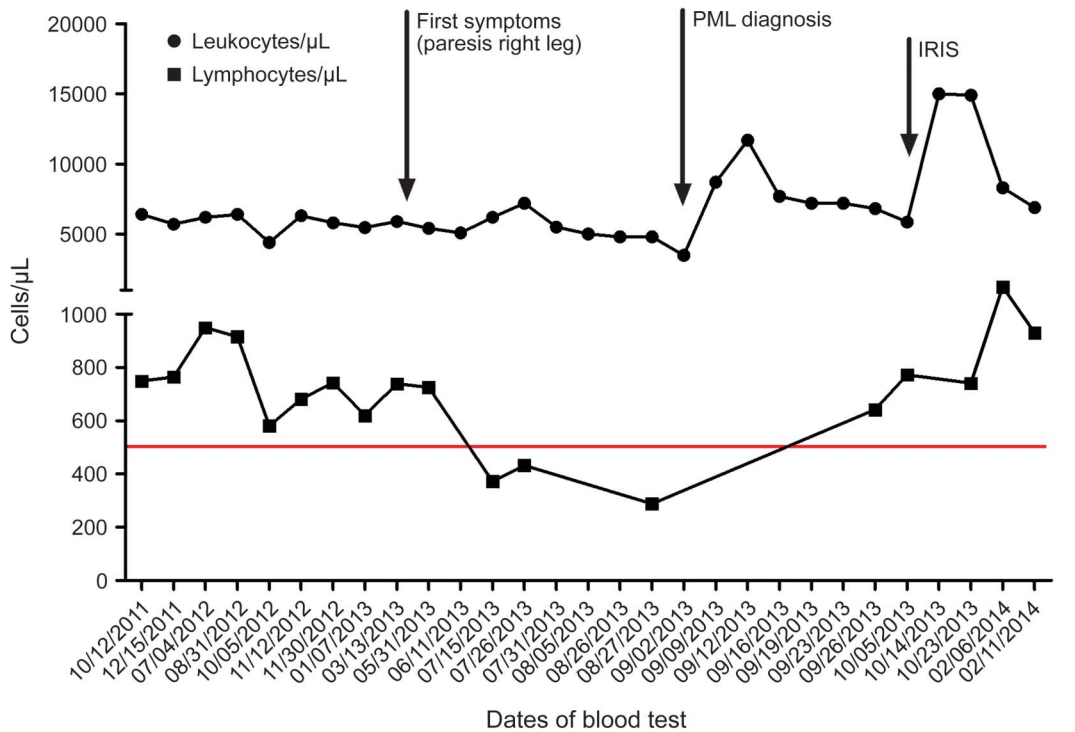
In September 2013, a 69-year-old Caucasian man who was anti–JC virus (JCV) antibody positive was admitted to our hospital with slowly progressing right hemiparesis and aphasia lasting for approximately 6 months. Medical history revealed arterial hypertension, biological aortic valve replacement, and psoriasis vulgaris, treated with 3–6 tablets daily of dimethylfumarate (DMF; 120 mg)/ethylhydrogenfumarate (EHF; 95 mg) (Fumaderm, Biogen Idec, Ismaning, Germany) since December 2008 (table e-1 at Neurology.org/nn). No other immunosuppressive pretreatment had been given. In April/May 2013, the patient recognized a steadily progressing weakness of the right leg. In June 2013, an external diagnosis of ischemic stroke was made. An MRI scan (figure e-1), which was performed after deterioration of clinical symptoms, revealed a subcortical left hemispheric lesion; biopsy demonstrated macrophage-dominated inflammation, dysmorphic astrocytes, simian virus 40 positivity, and several p53- and MiB1-positive cells, suggestive of a JCV encephalitis (figure e-2). JCV DNA was detected in CSF at 2 different time points using a highly sensitive PCR protocol (September 24, 2013, 16 copies/mL; October 7, 2013, 42 copies/mL),[1] leading to the diagnosis of progressive multifocal leukoencephalopathy (PML) in September 2013. Further diagnostic workup (table e-2) unmasked toxic bone marrow damage (figure e-3) and an increased excretion of kappa light chains in urine without any evidence for a plasmocytoma. Taking into account the patient's initial presentation with a slowly progressive paresis since April/May 2013 as well as the initial MRI scan (figure e-1), which is compatible with the PML diagnosis, we believe that the onset of PML was in April/May without preexisting leukopenia and only moderate lymphopenia (grade 2 lymphopenia: 724–738 cells/μL, figure). Several weeks

Figure Leukocyte and lymphocyte counts



IRIS = immune reconstitution inflammatory syndrome; PML = progressive multifocal leukoencephalopathy.

Supplemental data at Neurology.org/nn

later, white blood cell count dropped to a minimum of 4,800 cells/μL with 288 cells/μL lymphocytes under continuous Fumaderm treatment. Fumaderm was discontinued, and treatment with mirtazapine (45 mg/day; Remergil, MSD Sharp und Dohme GmbH, Haar, Germany), mefloquine (250 mg/week; Lariam, Roche Pharma AG, Grenzach-Wyhlen, Germany), and levetiracetam (1,000 mg/day; Keppra, UCB Pharma GmbH, Monheim, Germany) was initiated.[2]

One month later, a mild immune reconstitution inflammatory syndrome (IRIS) occurred, with deterioration of the hemiparesis (Karnofsky index [KI] 50%) accompanied by gadolinium enhancement on MRI. Two IV methylprednisolone treatments (each 500 mg/day for 3 days) were given. In June 2014, hemiparesis and aphasia had improved (KI 90%), JCV CSF PCR was negative, and leukocyte and lymphocyte counts had normalized (8,310 cells/μL and 1,240 cells/μL, respectively). Cerebral MRI scan was stable.

In contrast to the previously described cases of Fumaderm- and Psorinovo-associated PML in psoriasis,[3,4] we present a case without a preexisting, long-standing, and severe leukopenia/lymphopenia (figure 1) or immunosuppressive pretreatment. In the absence of other discernable myelotoxic factors, bone marrow damage might have been related to Fumaderm treatment. Despite the diagnostic delay, disease course, including IRIS, was mild.[3–5] Further studies on potential myelotoxic effects of fumarates and specific effects of DMF vs EHF are warranted. Physicians treating multiple sclerosis patients with DMF should be vigilant for PML as a possible but rare side effect. A long-lasting and presumably severe lymphopenia may especially predispose patients to PML.

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