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LETTER TO THE EDITORS

Cerebellar manifestation of PML under fumarate and after efalizumab treatment of psoriasis

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Dear Sirs,

Fumaric acid, first applied topically in psoriasis, has also been used orally since the mid-1980s. A preparation of dimethyl fumarate, BG-12, reduces disease activity in multiple sclerosis (MS) [2] and has been licensed, with recent market introduction in Europe. Despite common lymphopenia, no serious opportunistic infections had been attributed to it before two recent cases of progressive multifocal leukoencephalopathy (PML) [1, 9], with two more cases on file with the manufacturer [8]. We report details of one of these additional cases.

A Caucasian man, diagnosed with psoriasis in 1995, received local corticosteroids and occasionally steroid tablets, vitamin D_3-analogues, UVB therapy, and acitretin. Treatment with efalizumab (2006–2007) was satisfactory, but discontinued for superficial spreading malignant melanoma on the cheek (Clark-level II, excision in sano). Oral fumarate (Fumaderm®, Biogen-Idec) was initiated in 2007 (Fig. 1, top panel).

He was referred in July 2010 with a two-month history of slurred speech, unstable walking, and progressive decline in left-sided coordination that eventually left him unable to climb stairs. Examination showed left-sided hemiataxia and dysarthria without motor, sensory, or cognitive impairment.

On brain magnetic resonance imaging (MRI, Fig. 1 bottom panel), lesions in the left cerebellar peduncle and pons enhanced with gadolinium. Polymerase chain reaction (qPCR) detected >2,000 copies of JCV-DNA/ml (Universities Leipzig, Düsseldorf) in the cerebrospinal fluid (CSF), which was otherwise normal. Peripheral blood analysis revealed lymphopenia, CD4+ T cell deficiency (131/µl), and reduced IgG concentration (Fig. 1, middle panel). After exclusion of malignoma, HIV, and tuberculosis, lymphopenia was regarded as fumarate-induced.

We discontinued fumarate, substituted immunoglobulin, and initiated mirtazapine [5] in August 2010. Clinical course stabilized and improved to walking for 20 min with bilateral assistance. In October 2010, an acute lower respiratory tract infection led to clinical worsening, but resolved with antibiotic treatment. In March 2011, JCV-PCR of CSF was reported negative (University Leipzig). In September 2011, walking distance decreased to 410 m with walking frame; brain MRI showed a new, non-enhancing lesion in the right cerebellar peduncle; CSF JCV-PCR detected 19 copies/ml (NIH), identifying only the virulent "prototype", with undetectable non-virulent "archetype". Since deterioration was gradual rather than acute, and in the absence of Gd-enhancing lesions, the relapse was not considered PML-associated "immune reconstitution induced syndrome" (PML-IRIS). Treatment with

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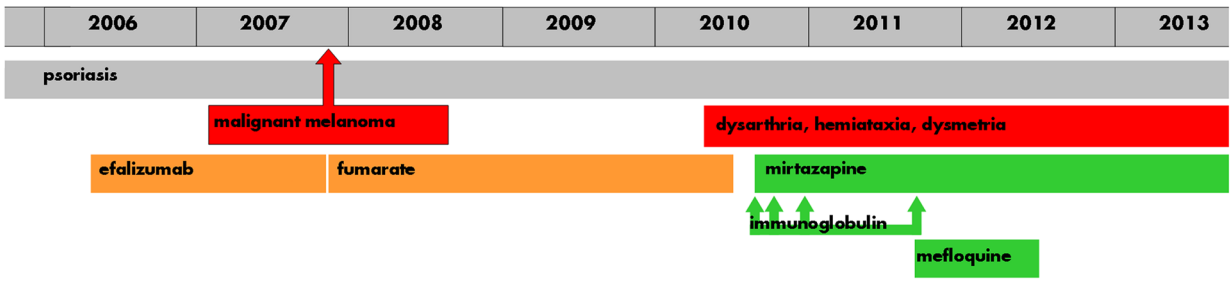
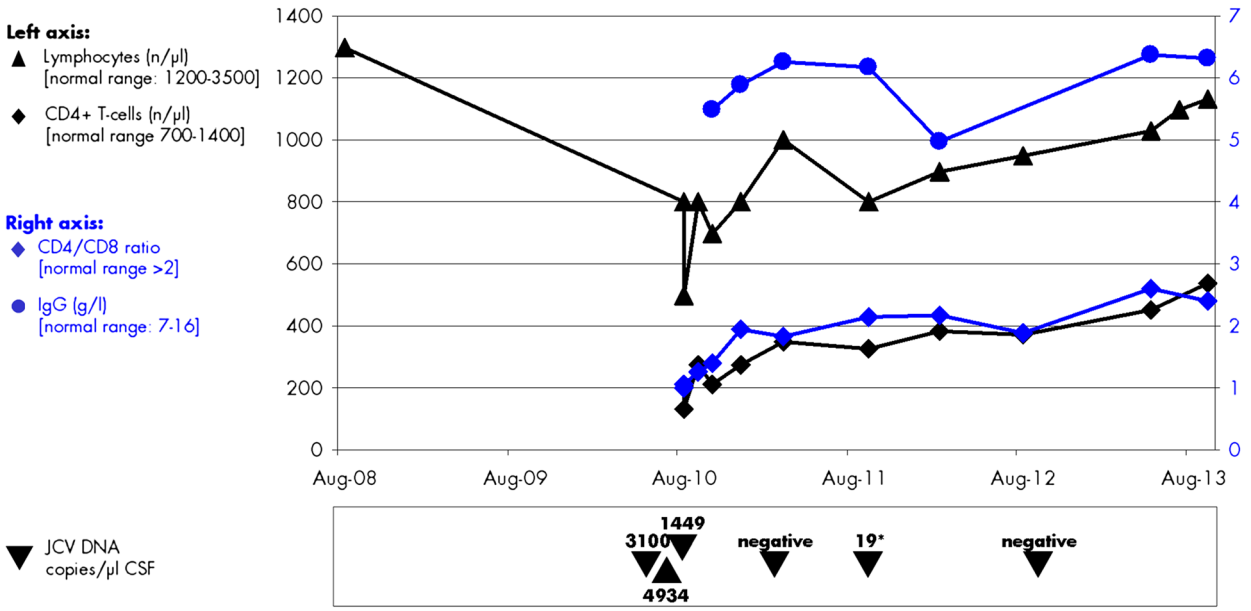
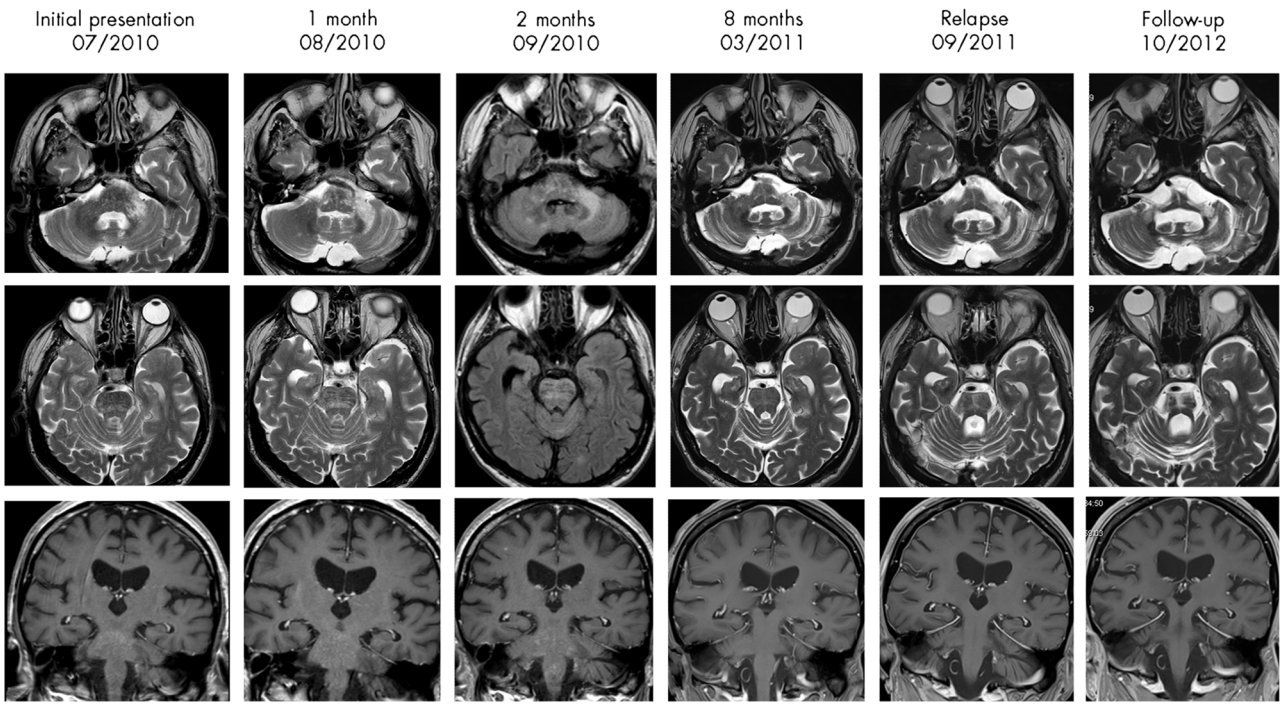

2006
2007
2008
2009
2010
2011
2012
2013
psoriasis
malignant melanoma
dysarthria, hemiataxia, dysmetria
efalizumab
fumarate
mirtazapine
immunoglobulin
mefloquine


Left axis:
Lymphocytes (n/µl) [normal range: 1200-3500]
CD4+ T-cells (n/µl) [normal range 700-1400]
Right axis:
CD4/CD8 ratio [normal range >2]
IgG (g/l) [normal range: 7-16]
1400
1200
1000
800
600
400
200
0
7
6
5
4
3
2
1
0
Aug-08
Aug-09
Aug-10
Aug-11
Aug-12
Aug-13
JCV DNA copies/µl CSF
1449
3100
4934
negative
19*
negative


Initial presentation 07/2010
1 month 08/2010
2 months 09/2010
8 months 03/2011
Relapse 09/2011
Follow-up 10/2012

◀**Fig. 1** *Top panel* Synopsis. Given are the major diagnoses and immunomodulatory treatments for psoriasis (*orange boxes*) and therapeutic interventions for PML (*green boxes* and *arrows*). *Middle panel* Results of laboratory investigations. Time course of peripheral blood counts for lymphocytes and CD4+ T lymphocytes (*left axis*), and CD4/CD8 ratio and serum IgG concentration (*right axis*). *Black triangles* indicate CSF analyses, with copy numbers for JCV DNA for each time point. At UKL, nucleic acid is extracted from CSF using magnetic beads, eluted in 50 µl, of which 5 µl is used in a 20 µl PCR reaction; first-step primers use common *VP2* gene sequences from BK and JC virus strains; positive samples are re-tested with primers from the *large-T-antigen* gene, differentiating BK and JC virus. At NIH, template extraction is performed using the Qiagen DNA spin column kit. In a qPCR reaction based on TaqMan® technology, a portion of the conserved, JCV-specific T protein coding sequence is amplified. A multiplex qPCR method simultaneously differentiates virulent from non-virulent JCV by detecting the NCRR specific for the virulent variant; this technique was employed on the CSF sample from Sep 2011 [6]. *Asterisk* this sample arrived at the NIH laboratory thawed; therefore, DNA may have partially degraded before analysis, and true copy number was presumably higher. In September 2012, the NIH detected 5 copies/ml. While the limit of detection in the NIH assay is 10 copies/ml, the 5 copies/ml were detected in duplicate runs and reported in that context. *Bottom panel* Magnetic resonance imaging. Transverse T2w images and coronal T1w images after administration of Gd contrast agent at the given time points. At two months, T2w images were inadequate due to pulsation artefacts and were, therefore, replaced by fluid attenuated inversion recovery (FLAIR) images. Note the atrophy of the cerebellum, the pons, and the middle cerebellar peduncles. The few supratentorial vascular white matter lesions, which never displayed Gd enhancement and remained unchanged during the entire course, are not shown.

mefloquine 250 mg/week was initiated and mirtazapine continued. Clinical condition improved during inpatient neurological rehabilitation and has been stable since February 2012. Mefloquine was discontinued on patient's request in June 2012. JCV-PCR of CSF in September 2012 was reported "undetectable", both at the UKL Leipzig and the NIH. MRI revealed moderate, progressive infratentorial brain atrophy. CD4+ lymphocyte count continues to increase slowly, not reaching reference range until September 2013 (540/µl).

Unlike typical PML, our patient had a purely infratentorial manifestation, with Gd-enhancement at presentation. Imaging in special forms of PML, JCV granule cell neuronopathy [3] and JCV encephalopathy [11], shows cerebellar atrophy or cortical lesions, but no white matter involvement or contrast-enhancement. The middle cerebellar peduncle lesion is in line with recently described infratentorial natalizumab-associated PML [10].

Fumarate-induced lymphopenia may have played an important part in the manifestation of PML. Efalizumab-associated PML presents after three or more years of treatment [4], similar to natalizumab-induced PML [7]; our patient was exposed to efalizumab for one year, but to fumarate for three. Clinical improvement followed fumarate discontinuation, paralleled by a continuous rise in CD4+ lymphocyte counts and the CD4/CD8 ratio. Although JCV serology or PCR were not performed before neurological manifestation, efalizumab may have enabled latent JCV infection of the brain—with fumarate-induced, long-term CD4+ T cell deficiency facilitating manifestation of PML. The gradual immune reconstitution may have prevented an acute PML-IRIS-induced clinical deterioration.

Manifestation of PML while on fumarate, with previous monoclonal antibody treatment, gains broader significance since the introduction of BG-12 for MS [2]. Especially patients treated with natalizumab for two years or longer may wish to discontinue use due to the increasing risk of PML. While oral fumarate is usually well-tolerated and safe, our case demonstrates that this sequence of treatments requires careful surveillance.

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Conflicts of interest The authors have no financial or other personal associations with respect to procedures, products, or findings mentioned in this report which could impose a conflict of interest.

Ethical standards Patient data were acquired during clinical care. The patient gave his written consent to report details as given in this manuscript.

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