A Case of Progressive Multifocal Leukoencephalopathy in a Fumaric Acid-Treated Psoriasis Patient With Severe Lymphopenia Among Other Risk Factors

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a potentially fatal condition caused by a brain infection with JC polyomavirus (JCV), which occurs almost exclusively in immunocompromised patients. Modern immunosuppressive and immunomodulatory treatments for cancers and autoimmune diseases have been accompanied by increasing numbers of PML cases. We report a psoriasis patient treated with fumaric acid esters (FAEs) with concomitant hypopharyngeal carcinoma and chronic alcohol abuse who developed PML. Grade 4 lymphopenia at the time point of PML diagnosis suggested an immunocompromised state. This case underscores the importance of immune cell monitoring in patients treated with FAEs, even more so in the presence of additional risk factors for an immune dysfunction.

KEYWORDS: progressive multifocal leukoencephalopathy, psoriasis, fumaric acid esters, carcinoma

TYPE: Case Report

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Case Report

A 52-year-old man presented to our neurological department in March 2020 reporting progressive limb ataxia and cognitive impairment including disorientation, attention and memory deficits, and reduced speech fluency since January 2020. Cranial magnetic resonance imaging (MRI) showed multifocal T2w-hyperintense white-matter lesions without contrast-enhancement, edema, or restricted diffusion predominantly involving the cerebellum (Figure 1). Cerebrospinal fluid (CSF) analysis revealed an elevation of protein levels with presence of CSF-specific oligoclonal IgG-bands and an increased CSF/serum albumin quotient as a marker of blood–brain barrier disruption, whereas the cell count was normal. The detection of 144 copies/mL of the JC virus (JCV) in CSF by polymerase chain reaction prompted the diagnosis of progressive multifocal leukoencephalopathy (PML).

During the previous 24 months, the patient's psoriasis was being treated with fumaric acid esters (FAEs) (Fumaderm®). During this time, lymphocyte counts were below 500/mm^3 in all routine measurements (Figure 2). At the time of PML diagnosis, the lymphocyte count was 147/mm^3 consistent with severe grade 4 lymphopenia, whereas the leukocyte count was within normal ranges. Furthermore, the patient had been diagnosed with hypopharyngeal carcinoma in July 2018, for which he received chemotherapy with 5-fluorouracil and cisplatin (from August 2018 until October 2018 with adjuvant radiation in weeks 1 and 5), nivolumab (3 cycles from April 2019 until May 2019), and docetaxel (6 cycles from July 2019 until October 2019). The clinical history included chronic alcohol and nicotine abuse (Figure 2).

After the PML diagnosis, FAE therapy was discontinued immediately. In addition, we initiated an off-label treatment attempt with mefloquine 250 mg per week and mirtazapine 15 mg per day based on *in vitro* data showing antiviral effects[1,2] and observations from several case reports (see Table 1). We stress that this treatment regimen has not convincingly prolonged survival or reduced disability in clinical trials so far.[3-6]

During this course of treatment, there was a gradual rise of lymphocyte counts without clinical evidence of immune reconstitution inflammatory syndrome; CSF analysis 3 weeks after PML diagnosis already showed a slight decrease in JCV DNA levels (117 copies/mL). Clinically, the patient experienced improvement of cognitive function, but significant limb ataxia persisted. MRI follow-up examination revealed regression of the cerebellar lesions (Figure 1). Serum neurofilament light chain (sNfL) levels were 149.9 pg/mL at PML diagnosis and constantly declined over the follow-up measurements 1, 2, and 3 months after diagnosis (Figure 2). There were no serum samples available to assess sNfL levels prior to PML diagnosis. sNfL was shown to serve as a non-specific biomarker of PML in

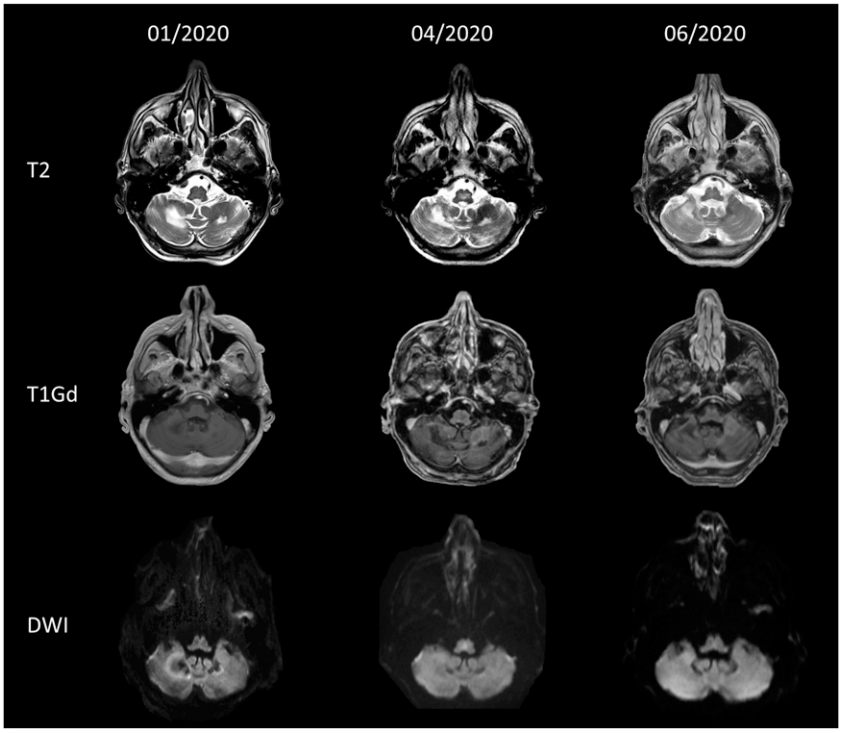

Figure 1. Magnetic resonance imaging findings over time. Upper row: T2-weighted axial images show hyperintense white-matter lesions in the cerebellum. Middle row: Axial T1 gadolinium (Gd)-weighted images show no Gd-enhancement. Lower row: Axial diffusion weighted image shows no restricted diffusion.

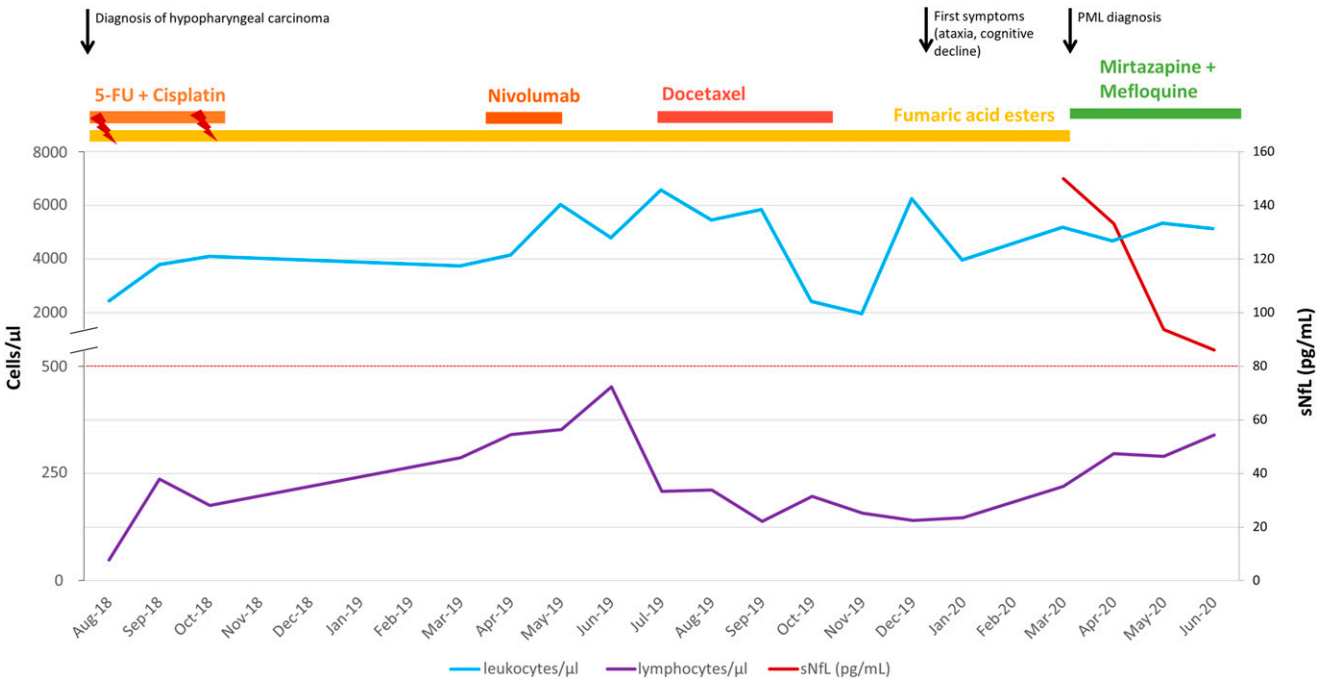

Figure 2. Overview of the patient's history and serum neurofilament light chain values. Leukocyte counts are displayed as a blue line. Lymphocyte counts are displayed as a violet line. Clinical events (black arrows) are indicated. Duration of treatments is depicted with lines of different colors on the top of the diagram. Serum neurofilament light chain levels are displayed as a red line.

natalizumab-treated multiple sclerosis (MS) patients[7,8] discriminating patients with PML from those without PML with high accuracy in a retrospective study.[7] A recent study in a prospective cohort confirmed that sNfL levels can identify natalizumab-treated MS patients who will develop PML with a sensitivity of 67% and specificity of 80%.[9] These results

Table 1. Overview of previous PML reports in FAE-treated psoriasis patients.

CASE REFERENCE	AGE, SEX	UNDERLYING CONDITIONS WITH IMMUNOCOMPROMISING POTENTIAL	DURATION OF FAE TREATMENT PRIOR TO PML ONSET	OTHER IMMUNOSUPPRESSIVE TREATMENTS WITHIN 5 YEARS PRIOR TO PML ONSET	GRADE OF LYMPHOPENIA[A] AT PML ONSET	DURATION OF LYMPHOPENIA PRIOR TO PML ONSET	PML TREATMENT	OUTCOME
Present case report	52-year-old male	Psoriasis, hypopharyngeal carcinoma, and alcohol abuse	2 years	Chemotherapy with 5-fluorouracil and cisplatin (terminated 17 months prior to PML onset), nivolumab (last cycle 10 months prior to PML onset), and docetaxel (terminated 5 months prior to PML onset)	4	18 months	Discontinuation of FAE treatment and off-label use of mirtazapine and mefloquine	Partial recovery from clinical symptoms, remission of MRI lesions, decrease in CSF JCV DNA titer and in sNfL levels
van Oosten et al (2013)[27]	42-year-old female	Psoriasis	5 years	None	3	5 years	Discontinuation of FAE treatment and off-label use of mirtazapine and mefloquine	Development of PML-IRIS followed by partial clinical recovery
Ermis et al (2013)[28]	74-year-old male	Psoriasis	3 years	Methotrexate (terminated 3 years prior to PML onset)	3	2 years	Discontinuation of FAE treatment and off-label use of mirtazapine and mefloquine	Development of PML-IRIS, followed by partial remission of clinical signs and MRI findings
Buttmann et al (2013), Sweetser et al (2013)[29,30]	60-year-old female	Psoriasis, and pulmonary sarcoidosis	3 years	Prednisolone and methotrexate (terminated 3.5 years prior to PML onset)	2–3	20 months	No information available	Partial recovery with mild-to-moderate residual symptoms
Stoppe et al (2014), Sweetser et al (2013)[15,30]	Male patient, no information on age available	Psoriasis, and superficial spreading melanoma	3 years	Efalizumab (terminated 3 years prior to PML onset)	2–3	No information available	Discontinuation of FAE treatment and off-label use of mirtazapine, mefloquine, and immunoglobulins	Partial recovery
Bartsch et al (2015)[12]	68-year-old male	Psoriasis, and adenocarcinoma of the rectum 8 years earlier (adjuvant radiochemotherapy with 5-fluorouracil)	2.5 years	None	2	16 months	Discontinuation of FAE treatment and off-label use of mirtazapine and mefloquine	Partial recovery

(Continued)

Table 1. Continued.

CASE REFERENCE	AGE, SEX	UNDERLYING CONDITIONS WITH IMMUNOCOMPROMISING POTENTIAL	DURATION OF FAE TREATMENT PRIOR TO PML ONSET	OTHER IMMUNOSUPPRESSIVE TREATMENTS WITHIN 5 YEARS PRIOR TO PML ONSET	GRADE OF LYMPHOPENIA[A] AT PML ONSET	DURATION OF LYMPHOPENIA PRIOR TO PML ONSET	PML TREATMENT	OUTCOME
Nieuwkamp et al (2015)[13]	64-year-old female	Psoriasis	2 years	None	2	1 month	Discontinuation of FAE treatment and off-label use of mirtazapine, mefloquine, and steroids	Deceased
Dammeier et al (2015)[31]	53-year-old female	Psoriasis	1.5 years	None	2–3	No information available	Discontinuation of FAE treatment and off-label use of mirtazapine and mefloquine	Stable disease course with only mild residual deficits at 7-month follow-up
Hoepner et al (2015)[32]	69-year-old male	Psoriasis, and monoclonal gammopathy	4 years	None	2–3	At least 18 months	Discontinuation of FAE treatment and off-label use of mirtazapine and mefloquine	Development of mild PML-IRIS followed by partial recovery
Elsner et al (2020)[33]	58-year-old female	Psoriasis	4 years	No information available	No information available	No information available	Discontinuation of FAE treatment and antiviral treatment (not specified)	Persisting global aphasia and recurrent seizures
Case series by Gieselbach et al (2017)[14]	57-year-old male	Psoriasis	4 years	No information available	1–3	4 years	No information available	Survived
Case series by Gieselbach et al (2017)[14]	50-year-old female	Psoriasis	9 years	No information available	2–3	6 years	No information available	Survived
Case series by Gieselbach et al (2017)[14]	71-year-old male	Psoriasis	1.5 years	No information available	3	No information available	No information available	Survived
Case series by Gieselbach et al (2017)[14]	64-year-old female	Psoriasis, breast carcinoma (10 years prior to PML)	.5 years	Cyclophosphamide	3	No information available	No information available	Survived

Abbreviations: CSF: cerebrospinal fluid, DNA, desoxyribonucleic acid; FAE, fumaric acid ester; IRIS, immune reconstitution inflammatory syndrome; JCV, JC virus; PML, progressive multifocal leukoencephalopathy.
[a]Grade 1 lymphopenia = 800–100 cells per mm^3, Grade 2 lymphopenia = 500–800 cells per mm^3, Grade 3 lymphopenia = 500–200 cells per mm^3, Grade 4 lymphopenia <200 cells per mm^3.

highlight the value of sNfL as a biomarker in clinical practice to monitor the occurrence and early recognition of PML.

This patient had numerous risk factors for developing PML, but he exhibited severe lymphopenia for approximately 18 months (minimal lymphocyte count 48/mm^3) before emergence of neurological deficits. Lymphopenia is a known side effect of FAE and is more likely to occur with older age.[10] FAE therapy should be terminated if the lymphocyte count drops below 500/mm^3 (corresponding to grade 3 and grade 4 lymphopenia) as the risk for opportunistic infections increases.[11] Previous reports of PML in FAE-treated psoriasis patients show low lymphocyte counts in all patients (Table 1), although some patients only had grade 1 or grade 2 lymphopenia at the time point of PML diagnosis.[12,13] Nevertheless, marked lymphocyte reduction is a modifiable risk factor in the prevention of PML and the existing recommendations for regular lymphocyte monitoring upon FAE therapy should be followed rigorously.

A second aspect that has likely contributed to the immunocompromised state along with PML development in this patient is the presence of concomitant hypopharyngeal carcinoma with various chemotherapeutic treatments. Remarkably, three of the previously published FAE-treated psoriasis patients who developed PML also had a history of concomitant malignancy; two of them received chemotherapy.[12,14,15] It is therefore difficult to separate the contributing effect of the malignancy on immune dysfunction from the effect its chemotherapy exhibits.

The previous treatment with the PD-1 inhibitor nivolumab in this patient is a topic of special interest since checkpoint inhibitors are currently discussed as a promising therapeutic option for the treatment of PML. They are believed to target pathways that are involved in immune exhaustion and reinvigorate antiviral immunity by restoring the anti-JCV activity of CD4$^+$ and CD8$^+$ T cells.[16] In several case reports and a small-scope case series, PD-1 inhibitor treatment with nivolumab or pembrolizumab was associated with clinical improvements in some patients.[17-20] However, there are also reports of patients who developed PML after treatment with nivolumab,[21] and cases where PML deteriorated despite treatment with pembrolizumab.[22,23] Additional analyses revealed that checkpoint inhibitors seem to be most promising in patients with some detectable anti-JCV cellular immune response before treatment, whereas advanced PML and profound immune compromise are associated with a poor treatment response.[23] Of note, our patient's chronic alcohol abuse might represent an additional risk factor for PML development.[24-26]

Taken together, we believe that the case reported here represents an illustrative example of the complexity of FAE treatment in patients exposed to situations of generalized immunosuppression such as chemotherapies. In retrospect, it is evident that this patient had an increased risk for the development of an opportunistic infection in general, and for PML in particular. Likewise, it is also indisputable that the occurrence of hypopharyngeal carcinoma required an effective treatment. However, the initiation of chemotherapy should have prompted the reevaluation of FAE treatment, especially when the lymphocyte count dropped to critical levels. From our point of view, this highlights the need to educate FAE-prescribing physicians about lymphocyte monitoring and PML and emphasizes that they must closely coordinate their immunotherapy with other physicians involved such as the oncologist.

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