

BRIEF COMMUNICATION

Diagnostic delay in progressive multifocal leukoencephalopathy

Dhanashri P. Miskin¹, Long H. Ngo² & Igor J. Koralnik¹¹Division of Neuro-Immunology, Departments of Neurology and Medicine, Center for Virology and Vaccine Research, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts²Division of General Medicine and Primary Care Section for Research, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts**Correspondence**

Igor J. Koralnik, Division of Neuro-Immunology, Department of Neurology, Center for Virology and Vaccine Research, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, E/CLS-1005, 300 Brookline Avenue, Boston, 02215 MA. Tel: 617 735 4460; Fax: 617 735 4527; E-mail: ikoralni@bidmc.harvard.edu

Funding Information

This study was supported in part by NIH grants R01NS 047029 and 074995.

Received: 14 December 2015; Revised: 23 February 2016; Accepted: 29 February 2016

Annals of Clinical and Translational Neurology 2016; 3(5): 386–391

doi: 10.1002/acn3.301

Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system (CNS) caused by the polyomavirus JC (JCV). PML occurs in immunosuppressed patients with AIDS, hematological malignancies, organ transplant recipients, and in individuals with autoimmune diseases treated with immunomodulatory medications.¹

Patients with PML develop progressive neurologic dysfunction associated with brain lesions that are readily detected on brain magnetic resonance imaging (MRI). Diagnosis is established either by detection of JCV DNA by polymerase chain reaction (PCR) in the cerebrospinal fluid (CSF), or by brain biopsy showing demyelination, astrogliosis, viral inclusion in nuclei of oligodendrocytes, and lipid-laden macrophages.²

PML only occurs in approximately 4000 people per year in the US and Europe, and it is therefore considered

Abstract

We investigated delay in diagnosing progressive multifocal leukoencephalopathy (PML). The median time from initial symptom to diagnosis was 74 days (range 1–1643) in 111 PML patients seen at our institution from 1993 to 2015. Another diagnosis was considered before PML in nearly two-thirds, and more than three-quarters of patients suffered from diagnostic delay greater than 1 month, irrespective of their underlying immunosuppressive condition. Extended diagnostic delay occurred more frequently in patients with possible PML, and among HIV⁺ patients with higher CD4⁺ T-cell counts at symptom onset. Prompt diagnosis may improve survival of PML in so far as immune reconstitution can be effected, and prevent unnecessary interventions.

an orphan disease.³ Since it is a rare disease, physicians seldom encounter patients with PML. In addition, symptoms and neuroimaging findings may often mimic more common CNS diseases, such as stroke,⁴ brain tumor^{5,6}, or cerebral toxoplasmosis.⁷

The aims of this study were to determine the incidence of diagnostic delay as well as its predisposing factors, and impact on the clinical outcome.

Methods

To understand the obstacles to the timely establishment of PML diagnosis, we retrospectively reviewed the records of all cases of PML seen in the Neuro-infectious Diseases Clinic at our institution between 1993 and 2015. A total of 111 PML patients were included in the analysis. Asymptomatic PML patients whose diagnosis was made based on routine surveillance MRI (one patient with multiple sclerosis on natalizumab and one on dimethyl

fumarate) and nine PML patients without comprehensive records regarding onset of PML symptoms were excluded from the analysis.

PML diagnosis was established according to consensus terminology criteria.² Patients who had survived beyond 1 year of neurological symptom onset were considered PML survivors, and those who died within 1 year as PML progressors. Patients who were still alive, but had been followed up for less than 1 year of disease onset, were considered PML early.⁸

Diagnostic delay was defined as the time interval between initial presentation of PML symptoms reported by patient history to confirmation of PML diagnosis. Alternative diagnoses prior to PML were determined based on clinical work-up and interventions. A diagnostic delay less than 1 month was labeled as limited, between one and 3 months as intermediate, and greater than 3 months as extended.

All patients underwent at least one spinal tap, and possible PML was defined by the presence of clinical and imaging findings suggestive of PML, but with negative CSF JCV PCR and no histologic confirmation.² The date of diagnosis in possible PML patients was determined by the last date of negative CSF PCR for JCV. Definite PML was confirmed by the detection of JCV DNA in the CSF by PCR or by histologic diagnosis on the brain biopsy.

We reported median and range for continuous variables and percentage for categorical variables. We used nonparametric testing, Wilcoxon signed-rank test, to compare median estimates and Fisher's exact test for contingency analysis. A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism 5.0 software.

Results

The median time from initial symptom to diagnosis of PML among 111 patients was 74 days (range 1–1643) and did not differ significantly among 45 HIV⁻ patients (50 days) and 66 HIV⁺ patients (84 days). Table 1 depicts the clinical characteristics of all patients. Of the 111 patients, diagnostic delay was less than 1 month in 25 (22.5%), one to 3 months in 42 (37.8%), more than 3 months in 44 (39.7%) and greater than 1 year in 10 (9%).

The diagnosis of PML was established in 92 (82.9%) of the 111 PML patients by virologic and/or histologic criteria (definite PML) and in 19 (17.1%) using clinical-radiologic criteria (possible PML). There were more patients with possible PML in the extended delay (25%) as compared with limited delay (4%) category (*P* < 0.05).

PML progressors were more frequent in the intermediate delay category (62%) compared with the limited delay category (36%) and the extended delay category (13.6%).

Of all 111 patients, the initial PML symptom was coordination deficit in 31 (28%), motor deficit in 18 (16.2%), language deficit in 15 (13.5%), altered mental status in 14 (12.6%), visual disturbance in 9 (8.1%), seizure in 6 (5.4%), motor and sensory deficit in 5 (4.5%), headache in 4 (3.6%), behavioral changes in 3 (2.7%), sensory disturbance in 3 (2.7%), and slurred speech in 3 (2.7%).

There was no significant difference in the three categories of delay based upon the presenting neurologic symptom, date of diagnosis, gender, age, etiology of underlying immunosuppression or treatment for PML. However, among HIV⁺ patients, the CD4⁺ T-cell count at symptom onset was greatest in the extended delay group as compared with either the limited or intermediate delay groups (*P* < 0.0005). Specifically, of the 14 HIV⁺ patients with CD4⁺ T-cell counts >200 cells/ μ L at PML symptom onset, 64.3% were in the extended, compared to 21.4% in the intermediate and 14.3% in the limited delay groups.

We repeated those analyses including only the 92 patients with definite PML. Again, we observed the same findings with more PML progressors in the intermediate delay category compared with the limited and extended delay categories as with the entire group. The definite and possible PML groups did not differ in terms of age or gender. However, the median time to diagnosis was 58.5 days in the definite PML group compared with 187 days in the possible PML group. There was also a significantly higher percentage of HIV⁺ patients in the possible compared with the definite group, 17/19 (89.5%) versus 49/92 (53.3%), and the CD4⁺ T-cell count of HIV⁺ patients was significantly higher in the possible compared with the definite group.

Interestingly, of the 92 definite PML patients, 23 (25%) had one or two negative CSF PCR for JCV prior to positive virologic or histologic diagnosis. Of these 23 PML patients, 11 (47.8%) were in the extended, 9 (39.1%) in the intermediate, compared to 3 (13.1%) in the limited delay category.

The most common initial diagnoses which prompted additional work-up and delayed diagnosis of PML among all patients were vascular (33%) followed by infections other than PML (16%) and tumoral (14%). However, in HIV⁻ patients, a tumoral diagnosis came in second place (14%), before autoimmune (12%), peripheral nervous system (12%), and infections other than PML (9%). In HIV⁺ patients, a vascular etiology was still the most frequent initial diagnosis (30%), followed by infections other than PML (21%) and tumoral (13%). This is

Table 1. Clinical characteristics of progressive multifocal leukoencephalopathy (PML) patients according to their diagnostic delay.

	Diagnostic delay		
	Limited (<1 month) <i>N</i> = 25 (22.5%)	Intermediate (1–3 months) <i>N</i> = 42 (37.8%)	Extended (>3 months) <i>N</i> = 44 (39.7%)
Gender			
Male	16 (64)	29 (69)	36 (81.8)
Female	9 (36)	13 (31)	8 (18.2)
Median age at PML symptom onset (range)	52 (23–79)	47 (22–84)	45.5 (20–84)
PML diagnostic criteria			
Definite	24 (96)*	35 (83.33)	33 (75)*
Possible	1 (4)*	7 (16.67)	11 (25)*
PML diagnosis			
Clinical-radiologic	1 (4)*	7 (16.67)	11 (25)*
Virologic	16 (64)	23 (54.7)	27 (61.3)
Histologic	6 (24)	11 (26.2)	5 (11.4)
Virologic + histologic	2 (8)	1 (2.43)	1 (2.3)
PML Status			
Early	1 (4)	3 (7)	1 (2.3)
Progressor	9 (36)*	26 (62)*,**	6 (13.6)**
Survivor	15 (60)*	13 (31)*,**	37 (84.1)**
Initial PML symptom			
Coordination deficit	8 (32)	10 (24.03)	13 (29.5)
Motor deficit	3 (12)	7 (16.67)	8 (18.2)
Language deficit	4 (16)	7 (16.67)	4 (9.1)
Altered mental status	6 (24)	3 (7)	5 (11.4)
Visual disturbances	2 (8)	3 (7)	4 (9.1)
Seizures	2 (8)	1 (2.43)	3 (6.8)
Motor and sensory deficit	0	3 (7)	2 (4.5)
Headache	0	2 (4.8)	2 (4.5)
Behavioral changes	0	2 (4.8)	1 (2.3)
Sensory disturbances	0	2 (4.8)	1 (2.3)
Slurred speech	0	2 (4.8)	1 (2.3)
Underlying immunodeficiency			
HIV	12 (48)	23 (54.7)	31 (70.4)
Hematologic malignancy ¹	7 (28)	11 (26.2)	6 (13.6)
Hematologic disease ²	2 (8)	2 (4.8)	5 (11.4)
Rheumatologic disease ³	1 (4)	4 (9.5)	1 (2.3)
Other ⁴	1 (4)	2 (4.8)	0
Systemic malignancy ⁵	1 (4)	0	1 (2.3)
Multiple sclerosis on natalizumab	1 (4)	0	0
Median CD4 ⁺ T-cell count at PML onset (range)			
HIV ⁺ (<i>N</i> = 65)	75.5 (9–468)**	73 (4–266)	115 (6–587)**
HIV ⁻ (<i>N</i> = 38)	417 (110–936)	472 (41–1243)	244 (80–1704)
Treatment for PML			
Mirtazapine	9 (36)	17 (40.57)	19 (43.2)
None	7 (28)	11 (26.2)	14 (31.8)
Mirtazapine + Mefloquine	3 (12)	5 (12)	4 (9.1)
Cidofovir	0	3 (7)	6 (13.6)
Mirtazapine + ARA-C	1 (4)	3 (7)	0
Mefloquine	1 (4)	0	1 (2.3)
Mirtazapine + Cidofovir	0	2 (4.8)	0
Cidofovir + Interferon alpha	1 (4)	1 (2.43)	0
Mirtazapine + IL-2	1 (4)	0	0

(Continued)

Table 1. Continued.

	Diagnostic delay		
	Limited (<1 month) N = 25 (22.5%)	Intermediate (1–3 months) N = 42 (37.8%)	Extended (>3 months) N = 44 (39.7%)
ARA-C	1 (4)	0	0
ARA-C + Interferon alpha	1 (4)	0	0

Comparisons have been made across columns between the different categories of diagnostic delay.

* $P < 0.050$, ** $P \leq 0.005$.

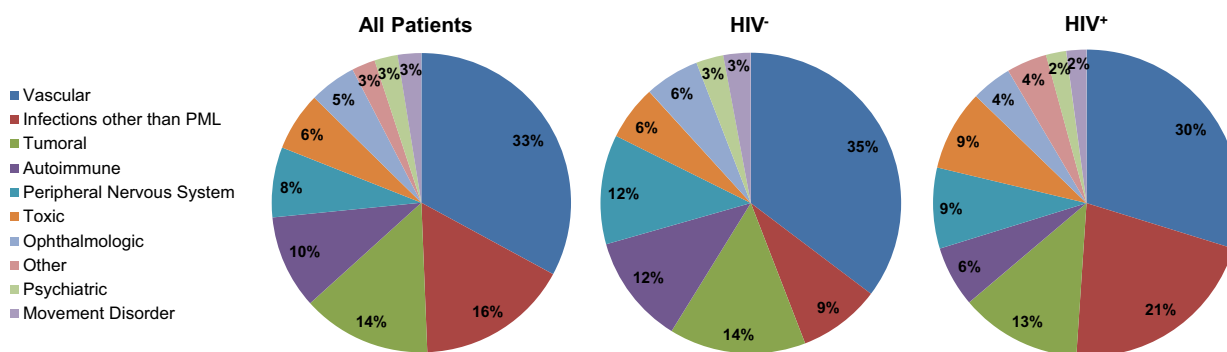
¹Chronic lymphocytic leukemia ($n = 11$), Non-Hodgkin's lymphoma ($n = 5$), Hodgkin's lymphoma ($n = 2$), B-cell lymphoproliferative disorder ($n = 2$), Acute myelogenous leukemia ($n = 1$), Anaplastic plasmacytoma ($n = 1$), Castleman's disease ($n = 1$), and NK cell leukemia ($n = 1$).

²Idiopathic CD4⁺ lymphocytopenia ($n = 5$), Waldenström's macroglobulinemia ($n = 2$), Good syndrome ($n = 1$), and Idiopathic thrombocytopenic purpura ($n = 1$).

³Rheumatoid arthritis ($n = 2$), Sarcoidosis ($n = 2$), Possible systemic lupus erythematosus ($n = 1$), and Dermatomyositis ($n = 1$).

⁴Combined variable immunodeficiency ($n = 1$), Idiopathic pulmonary fibrosis ($n = 1$), and Alcoholic cirrhosis ($n = 1$).

⁵Brainstem glioma ($n = 1$) and Non-small cell lung cancer ($n = 1$).



<p>Vascular</p> <ul style="list-style-type: none"> • Ischemic stroke • Cerebral vasculitis <p>Infections other than PML</p> <ul style="list-style-type: none"> • Toxoplasma encephalitis • HIV infection with associated encephalopathy • Varicella-zoster virus infection with associated small-vessel encephalitis or ophthalmic • Cerebritis • Intracerebral abscess • Lyme neuroborreliosis • Creutzfeldt-Jakob Disease <p>Tumoral</p> <ul style="list-style-type: none"> • Primary central nervous system lymphoma • Glioma • Metastasis • Paraneoplastic syndrome <p>Autoimmune</p> <ul style="list-style-type: none"> • Acute disseminated encephalomyelitis • Multiple sclerosis • Non-specific rheumatologic disease 	<p>Peripheral Nervous System</p> <ul style="list-style-type: none"> • Motor neuron disease • Neuromuscular junction disease • Radiculopathy • Guillain-Barré Syndrome <p>Toxic</p> <ul style="list-style-type: none"> • Radiation induced white matter disease • Chemotherapy induced white matter disease • Drug-induced adverse effect • Alcohol and substance abuse and/or withdrawal <p>Ophthalmologic</p> <ul style="list-style-type: none"> • Optic neuropathy • Unspecified blurry vision <p>Other</p> <ul style="list-style-type: none"> • Benign paroxysmal positional vertigo • Normal pressure hydrocephalus <p>Psychiatric</p> <ul style="list-style-type: none"> • Major depression <p>Movement Disorder</p> <ul style="list-style-type: none"> • Paroxysmal dyskinesia • Essential tremor
---	--

Figure 1. Initial diagnosis categories in progressive multifocal leukoencephalopathy patients.

depicted in greater detail in Figure 1. There were one, two, and three diagnoses considered prior to the diagnosis of PML in 64.4%, 25.4%, and 10.2% patients respectively.

Discussion

Diagnostic delay is detrimental to patients and incurs costs to the health care system as unnecessary testing is

performed and inappropriate treatments are prescribed. Delays or errors in diagnosis are also the most common and most costly malpractice claim.⁹ In addition, it causes great anxiety to patients and their families when they are given several consecutive diagnoses (stroke, brain tumor, autoimmune disease) prior to PML.

PML prognosis varies depending on comorbidities. Since there is no specific treatment for JCV, the management consists of treating the underlying cause of immunosuppression, or withdrawing potential immunosuppressive medications. Early intervention can improve the chance of survival and patients with limited diagnostic delay had a significantly better outcome than those in the intermediate category. However, the fact that the outcome was not worse among those with extended delay was surprising. It can be explained, in part, by the fact that 10/37 (27%) individuals in the extended delay category had their diagnosis established greater than 1 year after symptom onset, at which time they were already considered PML survivors. In addition, a greater percentage of patients in the extended delay category had possible PML. Those patients may have been better able to contain JC viral load in their CNS to levels undetectable by PCR in the CSF. Our results suggest that the better immune response at PML onset of the HIV⁺ possible PML patients was instrumental in limiting JCV replication to below detection levels by PCR in their CSF. Indeed, HIV⁺ patients in the extended delay category had higher initial CD4⁺ T-cell counts at time of PML onset. A low JC viral load in the CSF and higher CD4⁺ T-cell counts have been previously associated with a favorable clinical outcome in PML.^{8,10,11}

Since HIV infection is a classic form of immunosuppression predisposing to PML, we expected HIV⁺ patients to be more likely to have limited diagnostic delay compared with HIV⁻ individuals. Instead, there was a trend for HIV⁺ patients to be over-represented in the extended delay category. Since those patients had higher CD4⁺ T-cell counts at symptom onset compared with the limited and intermediate delay groups, these results suggest that physicians may disregard the diagnosis of PML in HIV⁺ patients with limited degree of immunosuppression. Furthermore, a vascular etiology, rather than infectious, was the most frequent initial diagnosis considered in HIV⁺ patients.¹²⁻¹⁴

Our study has limitations. Due to its retrospective nature, it is dependent on the quality and completeness of the patients' medical records spanning more than two decades. Most patients sought initial medical attention at their primary care physician's office, which was often outside our hospital. The diagnosis of PML may have been considered in the differential diagnosis then, but this information was not available. Other factors which may

have contributed to the delay in diagnosis include delay from PML symptom onset to first seeking medical attention, evaluation by a neurologist, obtaining initial MRI, performing a lumbar puncture, or arranging a brain biopsy. Detailed information about these factors was unavailable. In addition, exact time of PML symptom onset may be difficult to determine precisely. However, this was mitigated by the fact that the present cohort was collected at a single institution, and each patient was evaluated clinically by the same investigator (IJK). Only patients with complete clinical information were included in the study.

While the time of diagnosis is clearly established in patients with definite PML as the date of positive CSF JCV PCR or brain biopsy, it is more subjective in those with possible PML. All of the possible PML patients had one to three spinal taps and we chose the date of last negative CSF JCV PCR as time of diagnosis, after which all alternative entities had been ruled out. We and others have previously shown that patients with possible PML behave clinically and immunologically in a similar manner as those with definite PML, warranting their inclusion in observational studies.¹⁵ Furthermore, possible PML patients remain a significant diagnostic dilemma for physicians despite the improvement of PCR technique. In particular, MS patients developing PML during treatment with immunomodulatory medications often have undetectable JCV PCR in the CSF.^{16,17} Interestingly, there was no change in diagnostic delay based on the year of diagnosis, despite the gain in notoriety of PML after it was found in natalizumab-treated MS patients in 2005.

One patient included in our study had a significantly extended delay of 1643 days. It is noteworthy that a diagnosis of PML was considered in this patient 4 days after symptom onset based on clinical and radiological findings. However, initial CSF PCR for JCV was negative. He remained stable clinically and radiologically until 4.5 years later when he developed worsening depression and new auditory hallucinations. At that time, brain MRI revealed multiple new lesions concerning for PML and repeat CSF JCV PCR was positive, establishing a definitive diagnosis of PML.

Our data shows that another diagnosis was considered before PML in nearly two-thirds of patients, and more than three-quarters of PML patients suffered from diagnostic delay greater than 1 month, irrespective of their underlying immunosuppressive condition. Extended diagnostic delay occurred more frequently in patients with possible PML and among HIV⁺ patients with higher CD4⁺ T-cell counts at symptom onset. PML outcome was more favorable in patients with limited compared to intermediate diagnostic delay. Physicians should include JCV in the differential

diagnosis of patients presenting with neurological symptoms and brain lesions consistent with PML, regardless of their degree of immunosuppression.

Acknowledgment

This study was supported in part by NIH grants R01NS 047029 and 074995.

Conflicts of Interest

Dr. Miskin reports no disclosures or conflicts of interest. Dr. Ngo is funded by NIH grant R01 047029. Dr. Koralnik is funded by NIH grants R01 047029 and 074995; has received a research grant from Biogen Idec and the National Multiple Sclerosis Society; served on scientific advisory boards for Hoffmann La Roche, GlaxoSmithKline, Merck Serono, and MedImmune; received consulting fees from Bristol Myers Squibb, Ono Pharmaceuticals, Merck Serono, Hoffmann La Roche, GlaxoSmithKline, Perseid Therapeutics, Vertex Pharmaceuticals, and Johnson & Johnson; is an Associate Editor for the *Annals of Neurology*; and receives royalties from *UpToDate* for topics on the management of HIV and CNS mass lesions and on PML.

References

- Gheuens S, Wuthrich C, Koralnik IJ. Progressive multifocal leukoencephalopathy: why gray and white matter. *Annu Rev Pathol* 2013;24:189–215.
- Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN neuroinfectious disease section. *Neurology* 2013;80:1430–1438.
- Brew BJ, Davies NWS, Cinque P, et al. Progressive multifocal leukoencephalopathy and other forms of JC virus disease. *Nat Rev Neurol* 2010;6:667–679.
- Koralnik IJ, Schellingerhout D, Frosch MP. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 14-2004. A 66-year-old man with progressive neurologic deficits. *N Engl J Med* 2004;350:1882–1893.
- Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005;353:362–368.
- Gupta HV, Gokden M, Ramakrishnaiah RH, Archer RL. Progressive multifocal leukoencephalopathy mimicking glioma in a patient with idiopathic CD4 lymphocytopenia. *Acta Neurol Belg* 2015;[Epub ahead of print].
- Durel CA, Perpoint T, Makhloufi D, et al. Progressive multifocal leukoencephalopathy with immune reconstitution inflammatory syndrome misdiagnosed as cerebral toxoplasmosis in an HIV-infected woman. *Int J Infect Dis* 2015;36:70–71.
- Marzocchetti A, Tompkins T, Clifford DB, et al. Determinants of survival in progressive multifocal leukoencephalopathy. *Neurology* 2009;73:1551–1558.
- Saber Tehrani AS, Lee H, Mathews SC, et al. 25-Year summary of US malpractice claims for diagnostic errors 1986–2010: an analysis from the national practitioner data bank. *BMJ Qual Saf* 2013;22:672–680.
- Taoufik Y, Gasnault J, Karaterki A, et al. Prognostic value of JC virus load in cerebrospinal fluid of patients with progressive multifocal leukoencephalopathy. *J Infect Dis* 1998;178:1816–1820.
- Bossolasco S, Calori G, Moretti F, et al. Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. *Clin Infect Dis* 2005;40:738–744.
- Chow FC, Regan S, Feske S, et al. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. *J Acquir Immune Defic Syndr* 2012;60:351–358.
- Benjamin LA, Bryer A, Emsley HC, et al. HIV infection and stroke: current perspectives and future directions. *Lancet Neurol* 2012;11:878–890.
- Sacktor N. The epidemiology of human immunodeficiency virus-associated neurological disease in the era of highly active antiretroviral therapy. *J Neurovirol* 2002;8(Suppl 2):115–121.
- Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. *Lancet Neurol* 2010;9:425–437.
- Clifford DB, De Luca A, Simpson DM, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol* 2010;9:438–446.
- Bartsch T, Rempe T, Wrede A, et al. Progressive hemiparesis in a psoriasis patient treated with dimethyl fumarate. *Ann Neurol* 2015;78:501–514.