Drug-associated progressive multifocal leukoencephalopathy: a clinical, radiological, and cerebrospinal fluid analysis of 326 cases

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Abstract The implementation of a variety of immunosuppressive therapies has made drug-associated progressive multifocal leukoencephalopathy (PML) an increasingly prevalent clinical entity. The purpose of this study was to investigate its diagnostic characteristics and to determine whether differences herein exist between the multiple sclerosis (MS), neoplasm, post-transplantation, and autoimmune disease subgroups. Reports of possible, probable, and definite PML according to the current diagnostic criteria were obtained by a systematic search of PubMed and the Dutch pharmacovigilance database. Demographic, epidemiologic, clinical, radiological, cerebrospinal fluid (CSF), and histopathological features were extracted from each report and differences were compared between the disease categories. In the 326 identified reports, PML onset occurred on average 29.5 months after drug introduction, varying from 14.2 to 37.8 months in the neoplasm and MS subgroups, respectively. The most common overall symptoms were motor weakness (48.6 %), cognitive deficits (43.2 %), dysarthria (26.3 %), and ataxia (24.1 %). The former two also constituted the most prevalent manifestations in each subgroup. Lesions were more often localized supratentorially (87.7 %) than infratentorially (27.4 %), especially in the frontal (64.1 %) and parietal lobes (46.6 %), and revealed enhancement in 27.6 % of cases, particularly in the MS (42.9 %) subgroup. Positive JC virus results in the first CSF sample were obtained in 63.5 %, while conversion after one or more negative outcomes occurred in 13.7 % of cases. 52.2 % of patients died, ranging from 12.0 to 83.3 % in the MS and neoplasm subgroups, respectively. In conclusion, despite the heterogeneous nature of the underlying diseases, motor weakness and cognitive changes were the two most common manifestations of drug-associated PML in all subgroups. The frontal and parietal lobes invariably constituted the predilection sites of drug-related PML lesions.

Keywords Progressive multifocal leukoencephalopathy · Medication · Drugs · Side effect · Adverse event

Introduction

Progressive multifocal leukoencephalopathy (PML) is a JC virus (JCV) related demyelinating disorder of the central nervous system that occurs almost exclusively in immunocompromised patients [1]. It is characterized histopathologically by a lytic infection of oligodendrocytes, astrocytes, and/or neurons in the white matter, cortical gray matter, and/or gray-white matter junction giving
rise to a plethora of clinical phenotypes [2]. Quintessential radiological lesions are hyperintense on T2-weighted and FLAIR images and hypointense on T1-weighted images. In 2013, diagnostic criteria have been established which include clinical, imaging, laboratory, and histopathological features. Prerequisite for a definite diagnosis of PML is either the presence of characteristic pathoanatomic findings in a biopsy specimen or a combination of the appropriate clinical symptoms, radiological features, and the detection of JCV DNA in cerebrospinal fluid (CSF) [3]. Cases that do not fulfill these criteria might be classified as possible or probable PML and may be missed in official statistics.

PML has traditionally been associated with an intrinsically compromised immune system. In the past few years, a considerable number of immunosuppressive drugs has been approved by the authorities and implemented into clinical practice to broaden the therapeutic spectrum of a variety of medical conditions [4–6]. Consequently, medication-associated PML has become an increasingly prevalent clinical entity, as reflected by an exponential increase in the number of published cases (Fig. 1). Because of the frequently poor prognosis of PML, it is of paramount importance to establish this diagnosis at an early stage. However, a comprehensive, quantitative analysis of the clinical, radiological, and CSF features of drug-associated PML and its subgroups, based on the underlying disease categories, has never been conducted thus far. Nevertheless, for an early diagnosis it is crucial for clinicians across various specialties to be aware of the preferential clinical and radiological presentation and the potential differences herein between the subgroups. In this study, we aimed to address this urgent medical need for advances in knowledge on drug-associated PML by outlining its specific clinical, radiological, and CSF characteristics. A quantitative assessment of the degree of association between any particular drug and PML has been reported previously, and therefore fell beyond the scope of this paper [7].

Methods

Inclusion of published reports

References were identified by means of a three-step PubMed search conducted on August 30, 2015 (Fig. 2). To obtain a first inventory of the drugs that might trigger PML occurrence, the search terms ‘progressive multifocal leukoencephalopathy’, ‘drug induced’, ‘chemically induced’, ‘medication induced’, ‘adverse event’, ‘adverse effect’, and ‘side effect’ were used in the ‘all fields’ menu without limits of time. Second, combinations of ‘progressive multifocal leukoencephalopathy’ and the names of each of the individual drugs that had been identified in the first step were applied to collect all reports of potentially drug-associated PML. Finally, reference lists of all included articles were screened for any additional relevant reports.

We included cases of possible, probable, and definite PML according to the current American Academy of Neurology criteria [3] that were published in English language journals in case reports, case series, clinical trials, editorials, letters, meta-analyses, and observational studies. In addition, articles were included when they described a simultaneous immune reconstitution inflammatory syndrome (IRIS), either occurring already during treatment with or only after withdrawal of the causative drug. With respect to the latter, IRIS was defined as deterioration of neurologic deficits following drug removal, corroborated by inflammatory changes on neuroimaging [8]. Articles were excluded if an identical case had already been described in a previous report, when PML was not related to a drug, or if an alternative diagnosis was more likely, e.g., posterior reversible encephalopathy syndrome (PRES) associated with tacrolimus, cyclosporine, cisplatin, and methotrexate. Finally, cases of medication-related granule cell neuronopathy were excluded [9, 10]. When imaging features played a pivotal role in the distinction between ‘possible PML’ and ‘not PML’, the decision of inclusion or exclusion was made after analysis by an experienced neuroradiologist with special expertise in the field of inflammatory diseases of the central nervous system (MPW).
Dutch pharmacovigilance database

In addition to the cases published in the literature, reports on medication-associated PML were obtained by querying the database of the Netherlands Pharmacovigilance Centre Lareb. This database contains detailed accurately verified information of adverse drug reactions reported by Dutch healthcare professionals and manufacturers. Care was taken to exclude duplicates that had already been included in the literature search.
Data acquisition

The following data, when available, were extracted from each report: study type, number of cases, age, sex, underlying disease, immunosuppressive agent(s), time elapsed between drug introduction and either first symptoms or asymptomatic radiological findings that could be attributed to PML in retrospect, mortality rate (and time from first symptoms to death), and clinical, radiological, CSF, and histopathological features. When a combination of therapies rather than a single pharmaceutical was presumed to be responsible for the phenotype, the most likely contributing drugs—based on mechanism of action, dose, and duration of use—were noted up to a maximum of three. The localization of PML lesions was determined by the description provided by the authors of each report and the MR and/or CT images shown, if any. In addition, the presence of contrast enhancement, its distribution pattern (i.e., patchy, punctate, homogeneous, or unknown), and the dissemination pattern of lesions were listed. With respect to the latter, we distinguished between unilobar, multilobar (i.e., two or more contiguous lobes affected), and widespread (i.e., two or more noncontiguous lobes affected and/or the presence of lesions in both hemispheres). For the sake of clinical relevance and vigilance, symptoms and radiological lesions that appeared after establishing the diagnosis of PML, attributable to either progression of the disease or a consecutive emerging IRIS, were excluded.

Statistical analysis

Differences between the four subgroups, based on the underlying disease categories, were analyzed using Chi-square tests and one-way ANOVA. Post-hoc Bonferroni corrections have been applied and significance levels were set at 0.0083 (i.e., 0.05/6). Due to the conservative nature of the Bonferroni method [11], it seems likely that potential differences between the subgroups represent genuine dissimilarities rather than mere coincidence.

Results

Demographic and epidemiologic features

The literature search yielded 287 cases of drug-related PML in 184 case reports, 21 case series, 18 observational studies, three experimental studies, and two review articles [12–239]. Furthermore, an additional 39 reports were identified in the Dutch pharmacovigilance database, resulting in a total number of 326 documented cases. In eight cases, consensus was reached after initial doubt on the diagnosis of PML; five of them have been included, while the remaining three were finally labeled as ‘not PML’. Natalizumab, prednisolone, (dimethyl) fumarate, fludarabine, rituximab, and brentuximab vedotin were the most common single agents that have been demonstrated to trigger PML (Online Resource 1). Additionally, glucocorticoids with either azathioprine or cyclophosphamide and a regime containing four or more pharmaceuticals [usually courses of chemotherapy, frequently including rituximab (R-CHOP)] comprised the most prevalent composite culprits. The multifarious underlying diseases could be subdivided into four main categories, i.e. multiple sclerosis (MS), (other) immune-mediated disorders, neoplasms (93.8 % lymphoproliferative, 3.1 % myeloproliferative, 2.1 % solid neoplasm, 1.0 % unknown), and the post-transplantation setting (Fig. 3). Because of the relatively large number of natalizumab-associated PML cases, the former was not included in the group of immune-mediated diseases, but rather considered a distinct entity. As immunosuppressive drugs are also frequently used in the prevention of relapses in neuromyelitis optica spectrum disorder after a first episode, one might expect drug-associated PML to have been described in this patient population. However, no such reports have been identified in our search. The most common drugs associated with PML per subgroup are summarized in Online Resource 2. In general, there was considerably few drug overlap between the various disease categories, an exception being the combination of azathioprine and glucocorticoids which was used in both autoimmune disorders and the post-transplantation setting.

The age and sex distribution of drug-related PML among the subgroups were in accordance with the epidemiologic features of the particular diseases, with a higher percentage of younger women and older men in the MS and neoplasm subgroups, respectively (Table 1). The mean time elapsed from introduction of the drug(s) to first symptoms was 28.9 (95 % CI 25.5–32.2) months, while the time span to the occurrence of asymptomatic lesions (only in natalizumab-induced PML) was found to be 36.4 (95 % CI 27.0–45.9) months. Significantly shorter periods were observed in the neoplasm group [mean 14.2 months (95 % CI 9.3–19.2)] compared to the three other disease categories (p < 0.001). A delay of several weeks to even months between the occurrence of first symptoms and the final diagnosis of PML was noticed in a considerable number of cases [23, 28, 50, 67, 78, 101, 103, 117, 122, 149, 158, 185, 201, 213, 223, 224, 226, 233, 235, 236]. This diagnosis was established on combined clinical, radiological, and CSF grounds in 69.4 % of cases. In the remaining 30.6 %, histopathological analysis was necessary to provide a greater degree of certainty, either because PCR for JCV in the CSF was not available or (repeatedly) negative. Brain biopsies were conducted most commonly in patients with underlying autoimmune diseases (43.8 %) and neoplasms (47.8 %), but in only...
8.3% of natalizumab-induced PML cases. The overall mortality rate was 52.2% (95% CI 46.5–58.0%), with values of 12.0% (95% CI 5.2–18.7%), 56.2% (95% CI 44.5–67.8%), 83.3% (95% CI 75.5–91.2%), and 68.4% (95% CI 52.9–83.9%) in the MS, immune-mediated, neoplasm and post-transplantation subgroups, respectively.

Clinical characteristics

In descending order of magnitude, the most common overall symptoms and signs of drug-related PML were motor weakness (48.6%), cognitive deficits (43.2%), dysarthria (26.3%), ataxia (24.1%), aphasia (22.7%), and behavioral changes (21.9%) (Table 2). Although some deviations were observed between the subgroups, motor weakness and cognitive changes constituted the two most frequently encountered symptoms in all disease categories. Behavioral changes were significantly more common in the post-transplantation group than in any of the other disease categories (MS \( p < 0.001 \), immune-mediated disorders \( p = 0.001 \), neoplasms \( p = 0.002 \)). The highest prevalences of cognitive deficits and seizures were also found in this disease category (60.0 and 22.9%, respectively). Symptoms and signs of cerebellar and brainstem involvement, i.e., ataxia, vertigo, eye movement disorders, and dysphagia tended to be more prevalent in the group of autoimmune disorders. CML chronic myeloid leukemia, CLL chronic lymphocytic leukemia, GPA granulomatosis with polyangiitis (formerly Wegener’s disease), MDS myelodysplastic syndrome, NHL non-Hodgkin lymphoma, NSCLC non-small-cell lung cancer, RA rheumatoid arthritis, SLE systemic lupus erythematosus, WM Waldenström’s macroglobulinemia.
among the neoplasms was the high prevalence of visual deficits (25.8 %), especially when compared to the autoimmune disorders ($p = 0.001$). Asymptomatic PML cases were only observed in natalizumab-treated patients (10.3 %).

**Radiological findings**

Whereas infratentorial lesions were present in 27.4 % of cases, drug-associated PML was considerably more prevalent in the supratentorial brain (87.7 %) (Table 3). In all disease categories, lesions were most often situated in the frontal and parietal lobes (64.1 and 46.6 %, respectively). The temporal (21.4 %) and occipital (22.7 %) lobes were less commonly affected. Involvement of the latter, however, was observed relatively frequently in the neoplasm subgroup (36.2 %), in particular when compared to the autoimmune and MS groups ($p = 0.003$ and $p = 0.01$, respectively). Infratentorial lesion localization was especially prevalent in drug-related PML associated with immune-mediated disorders, with cerebellar involvement being significantly more common than in the MS and neoplasm categories ($p = 0.001$ and $p = 0.007$, respectively). Furthermore, there was a trend towards a higher level of brainstem involvement in the group of autoimmune diseases (MS $p = 0.013$; neoplasm $p = 0.077$). In the natalizumab-induced PML subgroup, lesions were most commonly distributed in one lobe (42.9 % vs. 21.4 % multilobar and 27.1 % widespread). In contrast, widespread dissemination was by far the most frequently encountered pattern in the remaining three disease categories (autoimmune disorders 52.5 %, neoplasms 52.1 %, post-transplantation 68.0 %). Contrast enhancement was present in 27.6 % of cases, particularly in the natalizumab-induced (42.9 %) and post-transplantation (31.6 %) subgroups. In the former, punctate and patchy enhancement patterns were observed to an equal extent (19.6 %). In the other subgroups, only patchy contrast enhancement was found.

**CSF results**

JCV DNA remained (repeatedly) undetectable in 22.7 % (95 % CI 17.3–28.1 %) of drug-associated PML cases. Furthermore, nearly one out of each seven patients (13.7 %; 95 % CI 9.3–18.1 %) initially displayed one or more negative outcomes before PCR finally converted to positive, ranging from 4.8 % in the post-transplantation (95 % CI 0.0–14.7 %) subgroup to 21.1 % (95 % CI
12.7–29.4 %) in the MS subgroup. Positive results in the first CSF sample were obtained in 63.5 %. Pleocytosis was present in 10.9 % of patients, especially in the neoplasm group (17.1 %).

**Discussion**

Despite the exponential increase in the number of drug-associated PML cases throughout the years, a comprehensive, quantitative analysis of its diagnostic characteristics that also takes into account the differences between the various underlying disease categories has not been performed thus far. Our study demonstrates that motor weakness and cognitive deficits are the most common presenting symptoms in all subgroups. Several dissimilarities were observed, however, between the disease categories in the remaining clinical manifestations. While behavioral and cognitive changes were most prevalent among the post-transplantation group, cerebellar and brainstem symptoms occurred most commonly in the autoimmune category. Visual disturbances appeared most frequently in drug-related PML associated with neoplasms. However, a sound explanation for these differences seems to be missing.

Because of the frequently grim prognosis and lethal outcomes, it is of paramount importance to consider the diagnosis of medication-associated PML at an early stage during treatment with immunosuppressive drugs. The clinical phenotype in the articles reviewed, however, was not seldom initially misinterpreted as an exacerbation or the cerebral manifestations of the underlying disease, i.e.,

| Table 2 Clinical characteristics of drug-associated progressive multifocal leukoencephalopathy |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Multiple sclerosis | Autoimmune diseases | Neoplasms | Post-transplantation | Total |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| (n = 87) | (n = 67) | (n = 89) | (n = 35) | (n = 278) |
| Motor weakness | 34 (39.1) | 34 (50.7) | 49 (55.1) | 18 (51.4) | 135 (48.6) |
| Cognitive deficits | 30 (34.5) | 25 (37.3) | 44 (49.4) | 21 (60.0) | 120 (43.2) |
| Dysarthria | 13 (14.9) | 25 (37.3) | 27 (30.3) | 8 (22.9) | 73 (26.3) |
| Ataxia | 14 (16.1) | 21 (31.3) | 23 (25.8) | 9 (25.7) | 67 (24.1) |
| Aphasia | 20 (23.0) | 19 (28.4) | 20 (22.5) | 4 (11.4) | 63 (22.7) |
| Behavioral change | 14 (16.1) | 12 (17.9) | 18 (20.2) | 17 (48.6) | 61 (21.9) |
| Gait abnormalities | 14 (16.1) | 18 (26.9) | 13 (14.6) | 5 (14.3) | 50 (18.0) |
| Visual deficits | 10 (11.5) | 4 (6.0) | 23 (25.8) | 6 (17.1) | 43 (15.5) |
| Sensory deficits | 7 (8.0) | 14 (20.9) | 5 (5.6) | 6 (17.1) | 32 (11.5) |
| Seizure | 9 (10.3) | 5 (7.5) | 6 (6.7) | 8 (22.9) | 28 (10.1) |
| Facial palsy | 5 (5.7) | 10 (14.9) | 6 (6.7) | 6 (17.1) | 27 (9.7) |
| Dysphagia | 2 (2.3) | 8 (11.9) | 6 (6.7) | 4 (11.4) | 20 (7.2) |
| Apraxia | 3 (3.4) | 3 (4.5) | 11 (12.4) | 2 (5.7) | 19 (6.8) |
| Vertigo | 4 (4.6) | 6 (9.0) | 3 (3.4) | 3 (8.6) | 16 (5.8) |
| Eye movement disorders | 2 (2.3) | 6 (9.0) | 8 (9.0) | 0 (0.0) | 16 (5.8) |
| Headache | 2 (2.3) | 3 (4.5) | 3 (3.4) | 3 (8.6) | 11 (4.0) |
| Parkinsonism | 1 (1.1) | 6 (9.0) | 2 (2.2) | 2 (5.7) | 11 (4.0) |
| Depression | 4 (4.6) | 2 (3.0) | 1 (1.1) | 1 (2.9) | 8 (2.9) |
| Asymptomatic | 9 (10.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 9 (3.2) |

Data have been displayed as frequency (percentage)

Because of the large number of natalizumab-associated PML cases, multiple sclerosis was considered a distinct entity and was not included in the group of autoimmune disorders

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an MS relapse, neuropsychiatric lupus, or central nervous system vasculitis [23, 28, 50, 67, 78, 101, 103, 117, 122, 149, 158, 185, 201, 213, 223, 224, 226, 233, 235, 236]. It was only after further clinical and radiological worsening upon high doses of immunosuppressive therapies that the possibility of PML was considered in these cases. Apart from the intrinsically dismal prognosis of PML, this delay of several weeks to even months and additional assault on the immune system certainly may have contributed to the high mortality rate. Sometimes, acute symptoms and signs were attributed to cerebral infarctions [21, 38, 109]. Finally, ocular and vestibular symptoms have occasionally been misjudged as cataract and Meniere’s disease, respectively [45, 120, 155]. It is possible that PML symptoms have been misinterpreted in these cases because of the relatively long interval between drug introduction and first central nervous system deficits, on average almost 2.5 years.

The differential diagnosis of medication-associated PML depends on the context in which the specific immunosuppressive drug is applied. In the post-transplantation setting, it is important to distinguish between drug-associated PML and PRES, which usually affects the parieto-occipital lobes and frequently resolves.

| Table 3 Radiological and cerebrospinal fluid features of drug-associated progressive multifocal leukoencephalopathy |
|---------------------------------------------------------------|
| **Radiological features**                                      |
| Multiple sclerosis a | Autoimmune diseases | Neoplasms | Post-transplantation | Total |
| Supratentorial       | 66/72 (91.7)        | 46/61 (75.4)* | 71/76 (93.4)* | 24/27 (88.9) | 207/236 (87.7) |
| Frontal lobe         | 49/69 (71.0)        | 32/57 (56.1)  | 43/69 (62.3)  | 17/25 (68.0) | 141/220 (64.1) |
| Parietal lobe        | 22/69 (31.9)        | 31/58 (53.4)  | 36/69 (52.2)  | 14/25 (56.0) | 103/221 (46.6) |
| Temporal lobe        | 9/69 (13.0)         | 12/57 (21.1)  | 21/69 (30.4)  | 5/25 (20.0)  | 47/220 (21.4)  |
| Occipital lobe       | 10/69 (14.5)*       | 9/57 (15.8)   | 25/69 (36.2)* | 6/25 (24.0)  | 50/220 (22.7)  |
| Basal ganglia        | 1/69 (1.4)          | 3/57 (5.3)    | 3/69 (4.3)    | 3/25 (12.0)  | 10/220 (4.5)   |
| Thalamus             | 3/69 (4.3)          | 6/58 (10.3)   | 8/69 (11.6)   | 3/25 (12.0)  | 20/221 (9.0)   |
| Capsula interna      | 3/69 (4.3)          | 4/59 (6.8)    | 2/69 (2.9)    | 3/25 (12.0)  | 12/222 (5.4)   |
| Corpus calosum       | 2/69 (2.9)          | 3/59 (5.1)    | 6/69 (8.7)    | 2/25 (8.0)   | 13/222 (5.9)   |
| Infratentorial       | 13/69 (18.8)*       | 25/60 (41.7)* | 15/69 (21.7)  | 8/25 (32.0)  | 61/223 (27.4)  |
| Cerebellum           | 8/69 (11.6)*        | 21/60 (35.0)* | 10/69 (14.5)* | 6/25 (24.0)  | 45/223 (20.2)  |
| Brain stem           | 7/69 (10.1)         | 16/59 (27.1)  | 10/69 (14.5)  | 5/25 (20.0)  | 38/222 (17.1)  |
| **Lesion distribution**                                     |
| Unilobar             | 30/70 (42.9)        | 13/59 (22.0)  | 13/71 (18.3)* | 1/25 (4.0)*  | 57/225 (25.3)  |
| Multilobar           | 15/70 (21.4)        | 13/59 (22.0)  | 17/71 (23.9)  | 6/25 (24.0)  | 51/225 (22.7)  |
| Widespread           | 19/70 (27.1)*       | 31/59 (52.5)* | 37/71 (52.1)* | 17/25 (68.0)*| 104/225 (46.2) |
| Unknown              | 6/70 (8.6)          | 2/59 (3.4)    | 4/71 (5.6)    | 1/25 (4.0)   | 13/225 (5.8)   |
| Contrast enhancement | 24/56 (42.9)*       | 5/43 (11.6)*  | 10/45 (22.2)  | 6/19 (31.6)  | 45/163 (27.6)  |
| Punctate             | 11/56 (19.6)*       | 0/43 (0.0)*   | 0/45 (0.0)*   | 0/19 (0.0)   | 11/163 (6.7)   |
| Patchy               | 11/56 (19.6)        | 3/43 (7.0)    | 8/45 (17.8)   | 4/19 (21.1)  | 26/163 (16.0)  |
| Homogeneous          | 1/56 (1.8)          | 0/43 (0.0)    | 0/45 (0.0)    | 0/19 (0.0)   | 1/163 (0.6)    |
| Unknown              | 1/56 (1.8)          | 2/43 (4.7)    | 2/45 (4.4)    | 2/19 (10.5)  | 7/163 (4.3)    |
| **CSF features**                                             |
| PCR JC virus        |
| Negative            | 11/95 (11.6)*       | 15/53 (28.3)  | 21/64 (32.8)* | 6/21 (28.6)  | 53/233 (22.7)  |
| Directly positive   | 64/95 (67.4)        | 31/53 (58.5)  | 39/64 (60.9)  | 14/21 (66.7) | 148/233 (63.5) |
| Positive after ≥2 LPs | 20/95 (21.1)*      | 7/53 (13.2)   | 4/64 (6.3)*   | 1/21 (4.8)   | 32/233 (13.7)  |
| **Leukocytes/ul**                                           |
| 0–4                 | 17/19 (89.5)        | 38/41 (92.7)  | 34/41 (82.9)  | 17/18 (94.4) | 106/119 (89.1) |
| ≥5                  | 2/19 (10.5)         | 3/41 (7.3)    | 7/41 (17.1)   | 1/18 (5.6)   | 13/119 (10.9)  |

Data have been displayed as frequency (percentage)

LP lumbar puncture
* e, # significant differences between subgroups (p < 0.05/6 = 0.0083)

a Because of the large number of natalizumab-associated PML cases, multiple sclerosis was considered a distinct entity and was not included in the group of autoimmune disorders.
spontaneously after withdrawal of the culprit(s). In MS patients, on the other hand, the distinction between a relapse and natalizumab-induced PML can be particularly troublesome. A correct and early diagnosis, however, has important therapeutic and prognostic implications. In this regard, several clinical and MRI features may direct the physician to the right diagnosis. Acute spinal cord or brainstem presentations and focal, sharp-edged, periventricular lesions are generally more frequently encountered in an MS exacerbation. In contrast, PML is characterized by a subacute onset, progressive nature of (sub)cortical symptoms, and large, ill-defined, confluent T2-weighted lesions, deep gray matter involvement, and/or crescent cerebellar lesions [240, 241]. This study confirms these findings, the most common natalizumab-associated PML symptoms being motor weakness, cognitive deficits, and aphasia, and lesions mainly localized in the frontal and parietal lobes. Isolated brainstem involvement, however, does not exclude PML at all [201, 233]. New imaging procedures such as the application of susceptibility weighted imaging and ultra high-field 7 Tesla MRI have shown promising preliminary data in the distinction between PML and MS lesions and might finally play a pivotal role when regular techniques fail to attain full assurance [242]. However, further work is required before they can be implemented in everyday clinical practice. 

Due to the raised level of radiological vigilance in natalizumab-treated patients including high-frequency MRI monitoring according to recent expert opinion guidelines [243, 244], cases of PML diagnosed at an asymptomatic stage are identified with increasing frequency [19, 27, 123, 137, 153, 162, 221]. These cases are only classified as probable PML in the presence of JCV DNA in the CSF detected by PCR, indicating the conservative nature of the current diagnostic criteria [3]. The predication of negative or inconclusive results across different laboratories in view of asymptomatic patients displaying MRI lesions has been touched upon previously [221] and stresses the need of a revision of the diagnostic PML criteria.

Definitive establishment of the PML diagnosis was hampered by initially negative PCR outcomes in CSF samples in nearly one out of each seven patients before it finally converted to positive. These results are strongly dependent on the disease stage and the characteristics of the assay, especially its lower detection limit, the sensitivity of the older assays being approximately 75 % [3]. Samples were frequently analyzed not only in the institute’s own laboratory, but also in external facilities, with the National Institutes of Health laboratory being the one with the most ultrasensitive assay (i.e., a detection limit of 10 JCV DNA copies per milliliter). Thus, physicians need to be aware that the lack of detection of JCV DNA in CSF does not preclude the diagnosis of PML. Repeated lumbar punctures, follow-up MRI, and possibly additional techniques currently under evaluation such as the assessment of anti-JCV antibodies in CSF [245], and in a proportion of cases, biopsy may be required to confirm the diagnosis of PML.

A clear radiological anterior-posterior gradient was observed, with the frontal and parietal lobes being more often involved than their temporal and occipital counterparts. A widespread lesion distribution pattern was found to be most common in drug-related PML associated with autoimmune disorders, neoplasms, and the post-transplantation setting, while (asymptomatic) unilobar involvement was most often observed in the natalizumab-induced subgroup. Contrast enhancement was present in about one fourth of cases of drug-associated PML, especially in the MS and post-transplantation subgroups. Although the underlying mechanisms and evolution of this ‘inflammatory PML’ variant remain to be elucidated, experimental evidence in natalizumab-induced PML suggests that lymphocyte trafficking continues to occur via alternative pathways due to upregulation of different adhesion molecules, thereby inducing a state of incomplete immune surveillance [246].

In contrast to what its name may suggest, the thalamus and basal ganglia—obviously deep gray matter structures—were involved in the PML disease process in 9.0 and 4.5 % of cases, respectively. Berger et al. previously demonstrated lesions in these areas in 14 and 12 % in PML associated with human immunodeficiency virus [247]. Furthermore, seizures which are generally assumed to be generated by synchronous cortical activity were present in 10.1 % of patients. In previous studies, even higher prevalences of 18 and 34.7 % were found, with causative PML lesions being situated adjacent to the T1-hyperintense cerebral cortical gray matter [248, 249]. It can be inferred from both observations that the ‘leukoencephalopathy’ phrase in the term PML, suggesting a white matter disease, is actually kind of a misnomer and rather confusing for clinicians who are not familiar with this disease.

The discrepancies in survival between the different categories of PML—not only the drug-associated cases, but also the ones related to an intrinsically compromised immune system—can probably be explained by their various degrees of ‘generalized’ immunosuppression. The more specific the immune system is targeted, the lower the mortality rate in general. We demonstrated a significantly lower mortality rate in the natalizumab-induced PML subgroup compared to the other disease categories and found the highest value in the neoplasm subgroup. As natalizumab impedes the interaction between alpha-4 integrin on lymphocytes and vascular cell adhesion molecule 1 on the endothelium of the vessel wall, it specifically
prevents the diapedesis of these cells through the blood-brain barrier without reducing the total number of leukocytes in the blood or their function. Therefore, in contrast to the various antineoplastic agents and immunosuppressive drugs used in cancer and the post-transplantation setting, the immune system may be more specifically suppressed. Depression of the immune system may not only result from the drugs administered, but is also an intrinsic consequence of the disease process in hematological malignancies which accounts for the highest mortality rate in this subgroup. Furthermore, the high level of radiological vigilance and occurrence of asymptomatic PML cases among MS patients treated with natalizumab frequently led to a quick drug suspension which probably contributed to a better prognosis.

Several intrinsic limitations of this study need to be addressed. Although we identified a large number of reports, not all cases of medication-related PML are published in the literature, especially when the association between the drug and the side effect has been described before. Therefore, our study design does not allow calculating the treatment-related risk of developing PML for each specific drug. Second, the contrast between underreporting in the oncology field on the one hand and the high clinical and radiological vigilance in MS and autoimmune disorders on the other has possibly led to a skewed distribution of published cases. Furthermore, the causal relationship between the mentioned drugs and PML may have been blurred by a variety of reasons. First, a state of immunosuppression could have already been present as a result of the underlying disease itself, e.g., due to lymphopenia in SLE, sarcoidosis, or leukemia. Indeed, PML has been described in these disorders in the absence of immunosuppressive medication [250, 251]. Therefore, it seems plausible to assume that PML in the group of neoplasms and in some but not all autoimmune disorders results from the interaction and synergistic immunosuppressive effects of the given drug(s) and the underlying disease. In the MS and post-transplantation setting, on the other hand, PML seems to be entirely attributable to iatrogenic reasons. Second, it is not inconceivable that several reports only mentioned the drug(s) that were taken at the time of PML onset, without giving notice to previous use of immunosuppressive therapies or long-standing leukopenia. As a result, the drugs mentioned may just have given the final push to the diagnosis of PML rather than being fully responsible. In most cases of this study (277/326, 85%), the risk of medication-associated PML seemed related to a maximum of three drugs. However, in this respect the heterogeneity of the data set needs to be appreciated and one should take into account several other factors like duration of treatment, concomitant medication use, and comorbidity.

In conclusion, drug-associated PML represents an emerging yet underrecognized clinical entity. We demonstrated that the various subgroups share several clinical and radiological characteristics despite the highly heterogeneous nature of the underlying diseases. In all subgroups, motor weakness and cognitive changes comprised the two most common clinical manifestations, while the frontal and parietal lobes invariably appeared to be the predilection sites of PML lesions. Nonetheless, it is important to be aware of subtle—and sometimes more obvious—differences in preferential presentations, e.g., discrepancies in the patterns of lesion dissemination and contrast enhancement. In the end, meticulous clinical and radiological vigilance in recognizing the phenotype at an early stage coupled with prompt withdrawal and clearance of the culprit, appropriate supportive therapies, and accurate monitoring and treatment of a consecutive IRIS remain crucial to obtain better outcomes in the battle against this frequently relentless disease.

Compliance with ethical standards

Ethical standards The manuscript does not contain clinical studies or patient data.

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References

1. Tan CS, Koralnik IJ (2010) Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol 9:425–437
2. Ghemius S, Wuthrich C, Koralnik IJ (2013) Progressive multifocal leukoencephalopathy: why gray and white matter. Annu Rev Pathol 8:189–215
3. Berger JR, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, Sejvar JJ, Bartt R, Major EO, Nath A (2013) PML diagnostic
criteria: consensus statement from the AAN neuroinfectious disease section. Neurology 80:1430–1438
4. Zaheer F, Berger JR (2012) Treatment-related progressive multifocal leukoencephalopathy: current understanding and future steps. Ther Adv Drug Saf 3:227–239
5. Molloy ES, Calabrese LH (2012) Progressive multifocal leukoencephalopathy associated with immunosuppressive therapy in rheumatic diseases: evolving role of biologic therapies. Arthritis Rheum 64:3043–3051
6. Mateen FJ, Muralidharan R, Carone M, van de Beek D, Harrison DM, Aksamit AJ, Gould MS, Clifford DB, Nath A (2011) Progressive multifocal leukoencephalopathy in transplant recipients. Ann Neurol 70:305–322
7. Schmedt N, Andersohn F, Garbe E (2012) Signals of progressive multifocal leukoencephalopathy for immunosuppressants: a disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System (AERS). Pharmacoepidemiol Drug Saf 21:1216–1220
8. Tan IL, McArthur JC, Clifford DB, Major EO, Nath A (2011) Immune reconstitution inflammatory syndrome in natalizumab-associated PML. Neurology 77:1061–1067
9. Wijburg MT, van Oosten BW, Murk JL, Karimi O, Killestein J, Wattjes MP (2015) Heterogeneous imaging characteristics of JC virus granule cell neuropathy (GCN): a case series and review of the literature. J Neurol 262:65–73
10. Wijburg MT, Siepmann D, van Eijk JJ, Killestein J, Wattjes MP (2016) Concomitant granule cell neuropathy in patients with natalizumab-associated PML. J Neurol 263:649–656
11. Eichstaedt KE, Kovatch K, Maroof DA (2013) A less conservative method to adjust for familywise error rate in neuropsychological research: the Holm’s sequential Bonferroni procedure. NeuroRehabilitation 32:693–696
12. Riskind PN, Richardson EP (1995) Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 20–1995. A 66-year-old man with a history of rheumatoid arthritis treated with adrenocorticosteroids, with the development of aphasia and right-sided weakness. N Engl J Med 332:1773–1780
13. Ahmed F, Aziz T, Kaufman LD (1999) Progressive multifocal leukoencephalopathy in a patient with systemic lupus erythematosus. J Rheumatol 26:1609–1612
14. Aksamit AJ Jr, de Groen PC (1995) Cyclosporine-related leukoencephalopathy and PML in a liver transplant recipient. Transplantation 60:874–876
15. Aksamit AJ Jr (2012) Progressive multifocal leukoencephalopathy. Continuum (Minneap Minn) 18:1374–1391
16. Al-Tawfiq JA, Banda RW, Daabil RA, Dawamneh MF (2015) Development of progressive multifocal leukoencephalopathy in a patient with non-Hodgkin lymphoma 13 years after treatment with cladribine. Leuk Lymphoma 54:1340–1342
17. Arbusow V, Strupp M, Pfister HW, Bruckmann H, Seelos KC, Bannykh S (2007) Progressive multifocal leukoencephalopathy in a patient with marginal zone B-cell lymphoma. J Neurooncol 85:289–290
18. Ayzenberg I, Lukas C, Bettaile G, Dughetti L, Ideo G, Sherna M (1993) Dysarthria and cerebellar ataxia: late occurrence of severe neurotoxicity in a liver transplant recipient. Transpl Int 6:176–178
19. Beppu M, Kawamoto M, Nukuzuma S, Kohara N (2012) Melfloquine improved progressive multifocal leukoencephalopathy in a patient with systemic lupus erythematosus. Intern Med 51:1245–1247
20. Berghoff M, Schanzer A, Hildebrandt GC, Dassinger B, Klappstein G, Kaps M, Gizewski ER, Acker T, Grams A (2013) Development of progressive multifocal leukoencephalopathy in a patient with non-Hodgkin lymphoma 13 years after treatment with cladribine. Leuk Lymphoma 54:1340–1342
21. Bartsch T, Rempe T, Wrede A, Leyboldt F, Bruck W, Adams O, Rohr A, Jansen O, Wuthrich C, Deuschl G, Koralinik IJ (2015) Progressive neurologic dysfunction in a psoriasis patient treated with dimethyl fumarate. Ann Neurol 78:501–514
22. Belli LS, De CL, Romani F, Rondinana GF, Romildo P, Alberti A, Battale G, Dughetti L, Ideo G, Sherna M (2013) Dysarthria and cerebellar ataxia: late occurrence of severe neurotoxicity in a liver transplant recipient. Transpl Int 6:176–178
23. Bartsch T, Rempe T, Wrede A, Leyboldt F, Bruck W, Adams O, Rohr A, Jansen O, Wuthrich C, Deuschl G, Koralinik IJ (2015) Progressive neurologic dysfunction in a psoriasis patient treated with dimethyl fumarate. Ann Neurol 78:501–514
24. Berghoff M, Schanzer A, Hildebrandt GC, Dassinger B, Klappstein G, Kaps M, Gizewski ER, Acker T, Grams A (2013) Development of progressive multifocal leukoencephalopathy in a patient with non-Hodgkin lymphoma 13 years after treatment with cladribine. Leuk Lymphoma 54:1340–1342
25. Berghoff M, Dassinger B, Iwinska-Zelder J, Giraldo M, Bilgin S, Kaps M, Gizewski ER (2014) A case of natalizumab-associated progressive multifocal leukoencephalopathy with cladribine. Leuk Lymphoma 54:1340–1342
26. Berghoff M, Schanzer A, Hildebrandt GC, Dassinger B, Klappstein G, Kaps M, Gizewski ER, Acker T, Grams A (2013) Development of progressive multifocal leukoencephalopathy in a patient with non-Hodgkin lymphoma 13 years after treatment with cladribine. Leuk Lymphoma 54:1340–1342
27. Berner B, Krieter DH, Rumpf KW, Grunewald RW, Beuache W, Weber T, Muller GA (1999) Progressive multifocal leukoencephalopathy in a renal transplant patient diagnosed by JCV-specific DNA amplification and an intrathecal humoral immune response to recombinant virus protein 1. Nephrol Dial Transplant 14:462–465
28. Blair NF, Brew BJ, Halpern JP (2012) Natalizumab-associated PML identified in the presymptomatic phase using MRI surveillance. Neurology 78:507–508
29. Boulton-Jones JR, Fraser-Moodie C, Ryder SD (2001) Long-term survival from progressive multifocal leukoencephalopathy after liver transplantation. J Hepatol 35:828–829
30. Bronshter DJ, Lidow MW, Wolfe D, Schwartz ME, Miller CM (2012) Excessively increased CSF tau in progressive multifocal leukoencephalopathy associated with immunosuppressive therapy. Ann Neurol 70:398–402
31. Bruggemann N, Gottschalk S, Kortke D, Marxsen JH, Moser A (2013) Case reports of PML in patients with natalizumab-associated PML. J Neurol 263:649–656
32. Buckanovich RJ, Liu G, Stricker C, Luger SM, Stadtmauer EA, Schuster SJ, Duffy K, Tsai D, Pruitt A, Porter DL (2002) Nonmyeloablative allogeneic stem cell transplantation for refractory Hodgkin’s lymphoma complicated by interleukin-2 responsive progressive multifocal leukoencephalopathy. Ann Hematol 81:410–413
33. Buttmann M, Stoll G (2013) Case reports of PML in patients treated for psoriasis. N Engl J Med 369:1081
34. Calvi A, De RM, Pietroboni AM, Ghezzi L, Maltese V, Arighi LB, Bookstaver PB, Sartor O, Bennett CL (2014) Progressive multifocal leukoencephalopathy: current understanding and future steps. Ther Adv Drug Saf 3:227–239
35. Carson KR, Newsome SD, Kim EJ, Wagner-Johnston ND, von Geldern G, Moskovitz CH, Moskovitz AJ, Rook AH, Jalan P, Loren AW, Landsburg D, Coyne T, Tsai D, Raisch DW, Norris LB, Bookstaver PB, Sartor O, Bennett CL (2014) Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: a report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project. Cancer 120:2464–2471
36. Cei M, Mumoli N, Ferrito G, Scazzero F (2010) Progressive multifocal leukoencephalopathy. South Med J 103:1074–1075
37. Chakraborty S, Tarantino SR, Treves J, Sambol D, Hauke RJ, Batra SK (2011) Progressive multifocal leukoencephalopathy in a HIV-negative patient with small lymphocytic leukemia following treatment with Rituximab. Case Rep Oncol 4:136–142
38. Chihara D, Takeoka T, Shirase T, Kishimoto W, Arimoto-Miyamoto K, Tsuji M, Ohno T (2010) Progressive multifocal leukoencephalopathy in myelodysplastic syndrome involving pure red cell aplasia. Intern Med 49:2347–2352
39. Choy DS, Weiss A, Lin PT (1992) Progressive multifocal leukoencephalopathy following treatment for Wegener’s granulomatosis. JAMA 268:600–601
40. Cid J, Revilla M, Cervera A, Cervantes F, Munoz E, Ferrer I, Montserrat E (2000) Progressive multifocal leukoencephalopathy following oral fludarabine treatment of chronic lymphocytic leukemia. Ann Hematol 79:392–395
41. Clerico M, Schiavetti I, De Mercanti SF, Piazza F, Gned D, Brescia MV, Lanzillo R, Ghezzi A, Bianchi A, Salemi G, Realmuñoz S, Sola P, Vitetta F, Cavalla P, Paolicelli D, Trojano M, Sormani MP, Durelli L (2014) Treatment of relapsing-remitting multiple sclerosis after 24 doses of natalizumab: evidence from an Italian spontaneous, prospective, and observational study (the TY-STOP Study). JAMA Neurol 71:954–960
42. Clifford DB, Ances B, Costello C, Rosen-Schmidt S, Andersson M, Parks D, Perry A, Yerra R, Schmidt R, Alvarez E, Tyler KL (2011) Rituximab-associated progressive multifocal leukoencephalopathy in rheumatoid arthritis. Arch Neurol 68:1156–1164
43. Coppo P, Laporte JP, Aoudjhane M, Lebon P, Isnard F, Lesage S, Gorin NC, Najman A (1999) Progressive multifocal leukoencephalopathy with peripheral demyelinating neuropathy after autologous bone marrow transplantation for acute myeloblastic leukemia (FAB).S. Bone Marrow Transplant 23:401–403
44. Crowder CD, Gyure KA, Drachenberg CB, Werner J, Morales RE, Hirsch HH, Ramos E (2005) Successful outcome of progressive multifocal leukoencephalopathy in a renal transplant patient. Am J Transplant 5:1151–1158
45. Cuevas LA, Fuchs HA (2004) Progressive multifocal leukoencephalopathy and immunosuppression. Ann Rheum Dis 63:112–113
46. D’Souza A, Wilson J, Mukherjee S, Jayesimi I (2010) Progressive multifocal leukoencephalopathy in chronic lymphocytic leukemia: a report of three cases and review of the literature. Clin Lymphoma Myeloma Leuk 10:E1–E9
47. Daibata M, Hatakeyama N, Kamioka M, Nemoto Y, Hiroi M, Miyoshi I, Taguchi H (2001) Detection of human herpesvirus 6 and JC virus in progressive multifocal leukoencephalopathy complicating follicular lymphoma. Am J Hematol 67:200–205
48. Damasceno A, von Glehn F, Martinez AR, Longhini AL, Deus-Silva L, Brandao CO, Santos LM, Damasceno BP (2011) Early onset of natalizumab-related progressive multifocal leukoencephalopathy. Mult Scler 17:1397–1398
49. Dannreuter N, Schubert V, Hauser TK, Bormann A, Bischof F (2015) Case report of a patient with progressive multifocal leukoencephalopathy under treatment with dimethyl fumarate. BMC Neurol 15:108
50. Dastmalchi M, Laki J, Lundberg IE, Iacobaeus E (2012) Progressive multifocal leukoencephalopathy in a patient with polymyositis: case report and literature review. J Rheumatol 39:1299–1303
51. Dawson DM (1982) Progressive multifocal leukoencephalopathy in myasthenia gravis. Ann Neurol 11:218–219
52. del Pilar Martin M, Cravens PD, Winger R, Kiesie BC, Cepok S, Edgar TN, Zamvil SS, Weber MS, Frohman EM, Klein-schmidt-DeMasters BK, Montine TJ, Hemmer B, Marra CM, Stuve O (2009) Depletion of B lymphocytes from cerebral perivascular spaces by rituximab. Arch Neurol 66:1016–1020
53. Desmond R, Lynch K, Glessen M, Farrell M, Murphy P (2010) Progressive multifocal leukoencephalopathy and cerebral toxoplasmosis in a patient with CLL. Am J Hematol 85:607
54. Dima D, Tomuleasa C, Irimie A, Florian IS, Petrushev B, Berindan-Neagoe I, Cucuianu A (2014) Magnetic resonance imaging-based diagnosis of progressive multifocal leukoen- cephalopathy in a patient with non-Hodgkin lymphoma after therapy with cyclophosphamide, doxorubicin, vincristine, prednison, and rituximab. Cancer 120:4005–4006
55. Dominguez-Mozo MI, Garcia-Montijo M, De Las Heras V, Garcia-Martinez A, Arias-Leal AM, Casanova J, Arroyo R, Alvarez-Lafuente R (2013) Anti-JCV antibodies detection and JCV DNA levels in PBMC, serum and urine in a cohort of Spanish Multiple Sclerosis patients treated with natalizumab. J Neuroimmunol Pharmacol 8:1277–1286
56. Egan JD, Ring BL, Reding MJ, Wells IC, Shuman RM (1980) Reticulum cell sarcoma and progressive multifocal leukoencephalopathy following renal transplantation. Transplantation 29:84–86
57. Elster MJ (2013) Natalizumab (tysabri)-associated progressive multifocal leukoencephalopathy: insights from perfusion magnetic resonance imaging. J Comput Assist Tomogr 37:694–697
58. Embrey JR, Silva FG, Helderman JH, Peters PC, Sagalowsky AI (1988) Long-term survival and late development of bladder cancer in renal transplant patient with progressive multifocal leukoencephalopathy. J Urol 139:580–581
59. Epker JL, van Biezen P, van Daele PL, van Gelder T, Vossen A, van Saase JL (2009) Progressive multifocal leukoencephalopa- thy, a review and an extended report of five patients with different immune compromised states. Eur J Intern Med 20:261–267
60. Ermis U, Weis J, Schulz JB (2013) PML in a patient treated with fumaric acid. N Engl J Med 368:1657–1658
61. Felli V, Di SA, Anselmi M, Gennarelli A, Sucapan P, Splendiani A, Catalucci A, Marini C, Gallucci M (2014) Progressive multifocal leukoencephalopathy following treatment with rituximab in an HIV-negative patient with non-hodgkin lymphoma. A case report and literature review. Neuroradiol J 27:657–664
62. Fianchi L, Colosimo C, De LA, Pompucci A, Cattani P, Voso MT, LaRocca LM, Leone G, Pagano L, Strollo C (2010) Atypical presentation of progressive multifocal leukoencephalopathy in a multiple myeloma patient after auto-SCT successfully treated with combination therapy. Bone Marrow Transplant 45:1668–1670
63. Fine AJ, Sorbello A, Kortepeter C, Scarazzini L (2014) Progressive multifocal leukoencephalopathy after natalizumab discontinuation. Ann Neurol 75:108–115
64. Fleischmann RM (2009) Progressive multifocal leukoencephalopathy following rituximab treatment in a patient with rheumatoid arthritis. Arthritis Rheum 60:3225–3228
65. Flomenbaum MA, Jarcho JA, Schoen FJ (1991) Progressive multifocal leukoencephalopathy fifty-seven months after heart transplantation. J Heart Lung Transplant 10:888–893
66. Focosi D, Fazzi R, Montanaro D, Emdin M, Petrini M (2007) Progressive multifocal leukoencephalopathy following treatment withrituximab in an HIV-negative patient with non-hodgkin lymphoma. J Neuroimmune Pharmacol 8:1277–1286
67. Fredericks CA, Kvam KA, Bear J, Crabtree GS, Josephson SA (2014) A case of progressive multifocal leukoencephalopathy in a lupus patient treated with belimumab. Lupus 23:711–713
68. Freim Wahl SG, Folvik MR, Torp SH (2007) Progressive multifocal leukoencephalopathy in a lymphoma patient with

[2] Springer
complete remission after treatment with cytostatics and rituximab: case report and review of the literature. Clin Neuropathol 26:68–73
69. Gajofatto A, Bianchi MR, Deotto L, Benedetti MD (2014) Are natalizumab and fingolimod analogous second-line options for the treatment of relapsing-remitting multiple sclerosis? A clinical practice observational study. Eur Neurol 72:173–180
70. Gaman A, Bold A, Gaman G (2011) The unexpected evolution of a case of diffuse large B-cell non-Hodgkin lymphoma. Rom J Morphol Embryol 52:719–722
71. García JH, Pearson J, Bonnin J, Gupta KL (1985) Deteriorating neurologic function in a 28-year-old renal transplant recipient. Ala J Med Sci 22:208–214
72. Garrote H, de la Fuente A, Ona R, Rodriguez I, Echevarría JE, Sepulveda JM, García JF (2015) Long-term survival in a patient with progressive multifocal leucoencephalopathy after therapy with rituximab, fludarabine and cyclophosphamide for chronic lymphocytic leukemia. Exp Hematol Oncol 4:8
73. Gedizlioglu M, Coban P, Cc P, Sivasli IE (2009) An unusual complication of immunosuppression in myasthenia gravis: progressive multifocal leucoencephalopathy. Neuromuscul Disord 19:155–157
74. Gentile S, Sacerdote I, Roccatallo D, Giordana MT (1996) Progressive multifocal leucoencephalopathy during cyclosporine treatment. A case report. Ital J Neurosurg 17:363–366
75. Giacomini PS, Rozenberg A, Metz I, Araujo D, Arbour N, Bar-Or A (2014) Maraviroc and JC virus-associated immune reconstitution inflammatory syndrome. N Engl J Med 370:486–488
76. Goldberg SL, Pecora AL, Alter RS, Kroll MS, Rowley SD, Waintraub SE, Imrit K, Preti RA (2002) Unusual viral infections (progressive multifocal leucoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 99:1486–1488
77. Gonzalez H, Bolgert F, Campoero P, Leblond V (1999) Progressive multifocal leucoencephalitis (PML) in three patients treated with standard-dose fludarabine (FAMP). Hematol Cell Ther 41:183–186
78. Govindappa V, Hicks S, Wichter M, Jolly M (2007) Progressive multifocal leucoencephalopathy in systemic lupus erythematosus. Arthritis Rheum 57:352–354
79. Grafl-Radford J, Robinson MT, Warsame RM, Matteson EL, Eggers SD, Keegan BM (2012) Progressive multifocal leucoencephalopathy in a patient treated with etanercept. Neurol Immunol Neuroinflammation 1:1
80. Grinyo J, Charpentier B, Pestana JM, Vanrenterghem Y, Vainchenker W, Imrit K, Preti RA (2002) Functional energetics of CD4+ T-cellular immunity in monoclonal antibody-associated progressive multifocal leukoencephalopathy. PLoS One 6:e18506
81. Hall WA, Martinez AJ, Dummer JS (1988) Progressive multifocal leucoencephalopathy after cardiac transplantation. Neurology 38:995–996
82. Harris HE (2008) Progressive multifocal leucoencephalopathy in a patient with systemic lupus erythematosus treated with rituximab. Rheumatology (Oxford) 47:224–225
83. Hasan MM, Taylor P (2005) Progressive multifocal leucoencephalopathy in a case of chronic lymphocytic leukaemia. Br J Haematol 130:808
84. Havla J, Berthele A, Kumpfel T, Krumholz M, Jochim A, Kronsbein H, Ryschkewitsch C, Jensen P, Lippmann K, Hemmer B, Major E, Hohlfeld R (2013) Co-occurrence of two cases of progressive multifocal leuкоencephalopathy in a natalizumab “infusion group”. Mult Scler 19:1213–1215
85. Heine A, Schmiedel A, Menschik T, Held SA, Ermann C, Brossart P (2013) Regression of liver metastases after treatment with oxaliplatin/capecitabine and development of a progressive multifocal leuкоencephalopathy in a patient with advanced thymoma. J Clin Oncol 31:e203–e205
86. Hendel-Chavez H, de Goer de Herve MG, Giannesini C, Mazet AA, Papeix C, Louapre C, Chardain A, Boutarfa N, Theaudin M, Adams D, Gasnault J, Stankoff B, Taoufik Y (2013) Immunological hallmarks of JC virus replication in multiple sclerosis patients on long-term natalizumab therapy. J Virol 87:6055–6059
87. Herold T, Seiler T, Egensperger R, Trumm C, Bergmann M, Franke D, Mum F, Schinwald N, Buske C, Dreyling M (2012) Progressive multifocal leucoencephalopathy after treatment with rituximab, fludarabine and cyclophosphamide in a patient with chronic lymphocytic leukemia. Leuk Lymphoma 53:169–172
88. Ho K, Garancis JC, Paegle RD, Gerber MA, Borkowski WJ (1980) Progressive multifocal leucoencephalopathy and malignant lymphoma of the brain in a patient with immunosuppressive therapy. Acta Neuropathol 52:81–83
89. Hoepner R, Faisser S, Klasing A, Schneider R, Metz I, Belbenberg L, Lukas C, Altmeier P, Gold R, Chan A (2015) Progressive multifocal leucoencephalopathy during fumarate monotherapy of psoriasis. Neuro Immunol Neuroinflammation 2:e85
90. Holmen C, Pehl F, Hillert J, Fogdell-Hahn A, Lundkvist M, Karlberg E, Nilsson P, Dahl C, Feltelius N, Svenningsson A, Lycke J, Olsson T (2011) A Swedish national post-marketing surveillance study of natalizumab treatment in multiple sclerosis. Mult Scler 17:708–719
91. Isidoro L, Pires P, Rito L, Cordeiro G (2014) Progressive multifocal leucoencephalopathy in a patient with chronic lymphocytic leukaemia treated with alemtuzumab. BMJ Case Rep. doi:10.1136/bcr-2013-201781
92. Itoh K, Kano T, Nagashio C, Mimori A, Kinoshita M, Sumiya M (2006) Progressive multifocal leucoencephalopathy in patients with systemic lupus erythematosus. Arthritis Rheum 54:1020–1022
93. Jones HR Jr, Hedley-Whyte ET, Friedberg SR, Kelleher JE Jr, Krokikowski J (1982) Primary cerebellopontine progressive multifocal leucoencephalopathy diagnosed premortem by cerebellar biopsy. Ann Neurol 11:199–202
94. Kalisch A, Wilhelm M, Erbguth F, Birkmann J (2014) Progressive multifocal leucoencephalopathy in patients with a hematological malignancy: review of therapeutic options. Chemotherapy 60:47–53
95. Kaufman GP, Aksamit AJ, Klein CJ, Yi ES, Delone DR, Litzow MR (2014) Progressive multifocal leucoencephalopathy: a rare infectious complication following allogeneic hematopoietic cell transplantation (HCT). Eur J Haematol 92:83–87
96. Khafan-Dabaja MA, Ayala E, Greene J, Rojiani A, Murtagh FR, Anasetti C (2007) Two cases of progressive multifocal leucoencephalopathy after allogeneic hematopoietic cell transplantation and a review of the literature. Bone Marrow Transplant 39:101–107
97. Khoury S, Shapira S, Ziberman T, Mekori YA, Hershko AY (2013) Progressive multifocal leucoencephalopathy in an HIV-negative patient following treatment with rituximab. Isr Med Assoc J 15:321–322
and CHOP chemotherapy in a patient with a diffuse large B-cell lymphoma. BMJ Case Rep. doi: 10.1136/bcr-2012-008142

192. Smolle E, Trojan A, Schuster SJ, Hayback J (2014) Progressive multifocal leukoencephalopathy—a case report and review of the literature. In Vivo 28:941–948

193. Sottini A, Capra R, Zanotti C, Chiarini M, Serana F, Ricotta D, Caimi L, Imberti L (2012) Pre-existing T- and B-cell defects in one progressive multifocal leukoencephalopathy patient. PLoS One 7:e34493

194. Sponzieri EE, Smith JK, Malamud N, McCulloch JR (1975) Progressive multifocal leukoencephalopathy: a complication of immunosuppressive treatment. Neurology 25:664–668

195. Stahl NI (2008) Progressive multifocal leukoencephalopathy in a minimally immunosuppressed patient with systemic lupus erythematosus treated with dapsone. J Rheumatol 35:725–727

196. Steurer M, Clausen J, Gotwald T, Gunsilius E, Stockhammer G, Gast G, Nachbaur D (2003) Progressive multifocal leukoencephalopathy after allogeneic stem cell transplantation and posttransplantation rituximab. Transplantation 76:435–436

197. Stoppe M, Thoma E, Liebert UG, Major EO, Hoffmann KT, Steurer M, Clausen J, Then BF (2014) Cerebellar manifestation of PML under fumarate and after efalizumab treatment of psoriasis. J Neurol 261:1021–1024

198. Taieb G, Renard D, Thouvenot E, Florid G (2002) Monoclonal antibody therapy with CAMPATH-1H in patients with non-Hodgkin’s lymphoma. Br J Haematol 119:317–322

199. Tomura N, Watanabe M, Kato T, Nishino K, Kowada M (1994) Transient punctuate enhancing lesions preceding natalizumab-associated progressive multifocal leukoencephalopathy. J Neurol Sci 134:10–14

200. Vulliemoz S, Lurati-Ruiz F, Borrow EA, Delavelle J, Koralnik IJ, Kunzer T, Bogousslavsky J, Picard F, Landis T, Du Pasquier RA (2006) Favourable outcome of progressive multifocal leukoencephalopathy in two patients with dermatomyositis. J Neurol Neurosurg Psychiatry 77:1079–1082

201. Wagner X, Martinu T, Palmer SM (2009) Progressive multifocal leukoencephalopathy following heightened immunosuppression after lung transplant. J Heart Lung Transplant 28:395–398

202. Wagner-Johnston ND, Bartlett NL, Cashen A, Berger JR (2012) Progressive multifocal leukoencephalopathy in a patient with Hodgkin lymphoma treated with brentuximab vedotin. Leuk Lymphoma 53:2283–2286

203. Warnatz K, Peter HH, Schumacher M, Wiese L, Prasse A, Petschner F, Vainh P, Volk B, Weiner SM (2003) Infectious CNS disease as a differential diagnosis in systemic rheumatic diseases: three case reports and a review of the literature. Ann Rheum Dis 62:50–57

204. Warth S, Hoenig PJ, Morris MJ, Teomete U, Benveniste R, Chapman JR, Losso IS (2012) Progressive multifocal leukoencephalopathy following treatment with bendamustine and rituximab. Int J Hematol 96:274–278

205. Wattjes MP, Verhoeff L, Zentjens W, Killestein J, van Munster ET, Barkhof F, van Eijk JJ (2013) Punctate lesion pattern suggestive of perivascular inflammation in acute natalizumab-associated progressive multifocal leukoencephalopathy: productive JC virus infection or preclinical PML-IRIS manifestation? J Neurol Neurosurg Psychiatry 84:1176–1177

206. Wattjes MP, Vulliemoz S, Lurati-Ruiz F, Borrow EA, Delavelle J, Koralnik IJ, Kunzer T, Bogousslavsky J, Picard F, Landis T, Du Pasquier RA (2006) Favourable outcome of progressive multifocal leukoencephalopathy in two patients with dermatomyositis. J Neurol Neurosurg Psychiatry 77:1079–1082

207. Wenning W, Haghikia A, Laubenberger J, Clifford DB, Behrens PF, Chan A, Gold R (2009) Treatment of progressive multifocal leukoencephalopathy: a multicenter phase I/II study. Ann Hematol 81:26–32

208. Wenning W, Haghikia A, Laubenberger J, Clifford DB, Behrens PF, Chan A, Gold R (2009) Treatment of progressive multifocal leukoencephalopathy: a multicenter phase I/II study. Ann Hematol 81:26–32

209. Wenning W, Haghikia A, Laubenberger J, Clifford DB, Behrens PF, Chan A, Gold R (2009) Treatment of progressive multifocal leukoencephalopathy: a multicenter phase I/II study. Ann Hematol 81:26–32
leukoencephalopathy associated with natalizumab. N Engl J Med 361:1075–1080
224. White RP, Abraham S, Sinhal S, Manji H, Clarke CR (2002) Progressive multifocal leukoencephalopathy isolated to the posterior fossa in a patient with systemic lupus erythematosus. Rheumatology (Oxford) 41:826–827
225. Worthmann F, Turker T, Muller AR, Patt S, Stoltenburg-Düding G (1994) Progressive multifocal leukoencephalopathy after orthotopic liver transplantation. Transplantation 57:1268–1271
226. Wuthrich C, Popescu BF, Gheuens S, Marvi M, Ziman R, Denq SP, Tham M, Norton E, Parisi JE, Dang X, Lucchinetti CF, Koralnik IJ (2013) Natalizumab-associated progressive multifocal leukoencephalopathy in a patient with multiple sclerosis: a postmortem study. J Neuropathol Exp Neurol 72:1043–1051
227. Yehia B, Davison A, Sisson S (2009) Transplant troubles. Am J Med 122:629–631
228. Yokoyama H, Watanabe T, Maruyama D, Kim SW, Kobayashi Y, Tobinai K (2008) Progressive multifocal leukoencephalopathy in a patient with B-cell lymphoma during rituximab-containing chemotherapy: case report and review of the literature. Int J Hematol 88:443–447
229. Zabernigg A, Maier H, Thaler J, Gatteringer C (1994) Late-onset fatal neurological toxicity of fludarabine. Lancet 344:1780
230. Zivadinov R, Dwyer MG, Hussein S, Carl E, Kennedy C, Zabernigg A, Maier H, Thaler J, Gattringer C (1994) Late-onset fatal neurological toxicity of fludarabine. Lancet 344:1780
231. ZuRhein GM, Varakis J (1974) Letter: progressive multifocal leukoencephalopathy in a renal-allograft recipient. N Engl J Med 291:798
232. Gheuens S, Smith DR, Wang X, Alsop DC, Lenkinski RE, Koralnik IJ (2012) Simultaneous PML-IRIS after discontinuation of natalizumab in a patient with MS. Neurology 78:1390–1393
233. Havla J, Hohlfeld R, Kumpfel T (2014) Unusual natalizumab-associated progressive multifocal leukoencephalopathy starting in the brainstem. J Neurol 261:232–234
234. Metz I, Radue EW, Oterino A, Kumpfel T, Wiendl H, Schippling S, Kuhle J, Sahraian MA, Gray F, Jakl V, Hauser D, Bruck W (2012) Pathology of immune reconstitution inflammatory syndrome in multiple sclerosis with natalizumab-associated progressive multifocal leukoencephalopathy. Acta Neuropathol 123:235–245
235. Eisele P, Szabo K, Hornberger E, Griebe M, Hennerici MG, Kieseier BC, Gass A (2014) Presumptive progressive multifocal leukoencephalopathy in multiple sclerosis after natalizumab therapy. J Neuroimaging 24:425–428
236. Blinkenberg M, Sellebjerg F, Leffers AM, Madsen CG, Sorensen PS (2013) Clinically silent PML and prolonged immune reconstitution inflammatory syndrome in a patient with multiple sclerosis treated with rituximab. J Clin Virol 49:519–523
237. Paues J, Vrethem M, Bates D, Edan G, Erakson M, Garcia-Merino A, Grigoriadis N, Hartung HP, Havrdova E, Hillert J, Hohlfeld R, Krencichutzky M, Lyon-Caen O, Miller A, Pozzilli C, Ravnborg M, Saida T, Sindic C, Vass K, Clifford DB, Hauser S, Major EO, O’Connor PW, Weiner HL, Clanet M, Gold R, Hirsch HH, Radu EW, Sorensen PS, King J (2011) Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurol 10:745–758
238. Sinnecker T, Othman J, Kuhl M, Mekle R, Selbig I, Niendorf T, Kunkel A, Wiencecke P, Kern P, Paul F, Faiss J, Wuerfel J (2015) 7T MRI in natalizumab-associated PML and ongoing MS disease activity: a case study. Neurol Neuroimmunol Neuroinflamm 2:e171
239. Wattjes MP, Rovira À, Miller D, Yousry TA, Sormani MP, de Stefano MP, Tintore M, Auger C, Tur C, Filippi M, Rocca MA, Zabernigg A, Maier H, Thaler J, Gattringer C (1994) Late-onset fatal neurological toxicity of fludarabine. Lancet 344:1780
240. Boster A, Hreha S, Berger JR, Bao F, Pennesta R, Tselis A, Endress C, Zuck I, Perumal J, Caon C, Vazquez J, Tyler KL, Racke MK, Millis S, Khan O (2009) Progressive multifocal leukoencephalopathy and relapsing-remitting multiple sclerosis: a comparative study. Arch Neurol 66:593–599
241. Kappos L, Bates D, Edan G, Erakson M, Garcia-Merino A, Grigoriadis N, Hartung HP, Havrdova E, Hillert J, Hohlfeld R, Krencichutzky M, Lyon-Caen O, Miller A, Pozzilli C, Ravnborg M, Saida T, Sindic C, Vass K, Clifford DB, Hauser S, Major EO, O’Connor PW, Weiner HL, Clanet M, Gold R, Hirsch HH, Radu EW, Sorensen PS, King J (2011) Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. Lancet Neurol 10:745–758
242. Sinnecker T, Othman J, Kuhl M, Mekle R, Selbig I, Niendorf T, Kunkel A, Wiencecke P, Kern P, Paul F, Faiss J, Wuerfel J (2015) 7T MRI in natalizumab-associated PML and ongoing MS disease activity: a case study. Neurol Neuroimmunol Neuroinflamm 2:e171
243. Watts MP, Rovira À, Miller D, Yousry TA, Sormani MP, de Stefano MP, Tintore M, Auger C, Tur C, Filippi M, Rocca MA, Fazekas F, Kappos L, Polman C, Barkhof F, Montalban X; MAGNIMS study group (2015) Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis-establishing disease diagnosis and monitoring patients. Nat Rev Neurol 11:597–606
244. McGuigan C, Craner M, Guadagno J, Kapoor R, Mazibradu G, Molynieux P, Nicholas R, Palace J, Pearson OR, Rog D, Young CA (2015) Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J Neurol Neurosurg Psychiatry 87:117–125
245. Warnke C, von Geldern G, Markwerth P, Dehmel T, Hoepner R, Gold R, Pawlita M, Kumpfel T, Maurer M, Stangel M, Wegner F, Hohlfeld R, Straeten V, Limbricht V, Weber T, Hermsen D, Kleinschnitz C, Hartung HP, Wattjes MP, Svenningsson A, Major E, Olsson T, Kieseier BC, Adams O (2014) Cerebrospinal fluid JC virus antibody index for diagnosis of natalizumab-associated progressive multifocal leukoencephalopathy. Ann Neurol 76:792–801
246. Schneider-Hohendorf T, R throttant J, Mohan H, Boding N, Breuer J, Kuhlmann T, Gross CC, Flanagan K, Sorokin L, Vestweber D, Zarbock A, Schwab N, Wiendl H (2014) VLA-4 blockade promotes differential routes into human CNS involving PSGL-1 rolling of T cells and MCAM-adhesion of TH17 cells. J Exp Med 211:1833–1846
247. Berger JR, Pall L, Lanska D, Whitehead M (1998) Progressive multifocal leukoencephalopathy in patients with HIV infection. J Neurovirol 4:59–68
248. Khoury MN, Alsop DC, Agnihotri SP, Pfannl R, Wuthrich C, Ho ML, Hackney D, Ngo L, Anderson MP, Koralnik IJ (2014) Hyperintense cortical signal on magnetic resonance imaging reflects focal leukocortical encephalitis and seizure risk in progressive multifocal leukoencephalopathy. Ann Neurol 75:659–669
249. Lima MA, Drislane FW, Koralnik IJ (2006) Seizures and their outcome in progressive multifocal leukoencephalopathy. Neurology 66:262–264
250. Davis MJ, Khan A, Royal W III (2013) Progressive multifocal leukoencephalopathy as the first manifestation of occult sarcoidosis: case report and review of the literature. Neurologist 19:26–29
251. Molloy ES, Calabrese LH (2008) Progressive multifocal leukoencephalopathy in patients with rheumatic diseases: are patients with systemic lupus erythematosus at particular risk? Autoimmun Rev 8:144–146