Journal of Clinical Immunology (2019) 39:55–64
https://doi.org/10.1007/s10875-018-0578-8

ORIGINAL ARTICLE

Progressive Multifocal Leukoencephalopathy in Primary Immunodeficiencies

Jérôme Hadjadj[1] · Aurélien Guffroy[2] · Christophe Delavaud[3] · Guillaume Taieb[4] · Isabelle Meyts[5,6] · Anne Fresard[7] · Nathalie Streichenberger[8] · Anne-Sophie L'Honneur[9] · Flore Rozenberg[9] · Maud D'Aveni[10] · Claire Aguilar[11,12] · Jérémie Rosain[13] · Capucine Picard[13,14,15] · Nizar Mahlaoui[12,15] · Marc Lecuit[11] · Olivier Hermine[1,12,14] · Olivier Lortholary[11,12] · Felipe Suarez[1,12,14]

Received: 3 September 2018 / Accepted: 3 December 2018 / Published online: 14 December 2018

Abstract

Purpose Progressive multifocal leukoencephalopathy (PML) is a rare but severe demyelinating disease caused by the polyomavirus JC (JCV) in immunocompromised patients. We report a series of patients with primary immune deficiencies (PIDs) who developed PML.

Methods Retrospective observational study including PID patients with PML. Clinical, immunological, imaging features, and outcome are provided for each patient.

Results Eleven unrelated patients with PIDs developed PML. PIDs were characterized by a wide range of syndromic or genetically defined defects, mostly with combined B and T cell impairment. Genetic diagnosis was made in 7 patients. Before the development of PML, 10 patients had recurrent infections, 7 had autoimmune and/or inflammatory manifestations, and 3 had a history of malignancies. Immunologic investigations showed $CD4^+$ lymphopenia (median 265, range 50–344) in all cases. Six patients received immunosuppressive therapy in the year before PML onset, including prolonged steroid therapy in 3 cases, rituximab in 5 cases, anti-TNF-α therapy, and azathioprine in 1 case each. Despite various treatments, all but 1 patient died after a median of 8 months following PML diagnosis.

Conclusion PML is a rare but fatal complication of PIDs. Many cases are secondary to immunosuppressive therapy warranting careful evaluation before initiation subsequent immunosuppression during PIDs.

✉ Felipe Suarez
felipe.suarez@aphp.fr

[1] Department of Haematology, Assistance Publique-Hôpitaux de Paris, Hôpital Necker-Enfants Malades, France et Université Paris Descartes, 149 rue de Sèvres, 75015 Paris, France

[2] Department of Clinical Immunology and Internal Medicine, National Reference Center for Autoimmune diseases, Hôpitaux Universitaires de Strasbourg, Strasbourg, France

[3] Department of Adult Radiology, Necker Hospital, Paris, France

[4] Department of Neurology, CHU Montpellier, Hôpital Guy de Chauliac, Montpellier, France

[5] Department of Microbiology and Immunology, Childhood Immunology, KU Leuven, Leuven, Belgium

[6] Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium

[7] Department of Infectious Diseases, CHU Saint-Etienne, Saint-Etienne, France

[8] Department of Pathology - Université Claude Bernard Lyon1 - Institut NeuroMyogène CNRS UMR 5310 - INSERM U1217, Hospices Civils de Lyon, Lyon, France

[9] Department of Virology, Université Paris Descartes et Assistance Publique-Hôpitaux de Paris, Hôpital Cochin, Paris, France

[10] Department of Hematology, University Hospital, Nancy, France

[11] Sorbonne Paris Cité, Necker Pasteur Center for Infectious Diseases and Tropical Medicine, APHP-Hôpital Necker-Enfants Malades, IHU Imagine, Université Paris Descartes, Paris, France

[12] Centre de Référence Déficits Immunitaires Héréditaires (CEREDIH), Hôpital Universitaire Necker-Enfants Malades, Paris Descartes University, Paris, France

[13] Study Center for Primary Immunodeficiencies, Necker-Enfants Malades Hospital, Assistance Publique Hôpitaux de Paris (APHP), Necker Medical School, Paris, France

[14] INSERM U1163 & CNRS ERL 8254, Institut Imagine, Sorbonne Paris Cité, Paris, France

[15] Pediatric Immuno-Haematology and Rheumatology Unit, Necker-Enfants Malades University Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France

Keywords Progressive multifocal leukoencephalopathy · polyomavirus JC · primary immunodeficiencies · combined immunodeficiencies · immunosuppressive therapy

Abbreviations

PID	Primary immune deficiency
PML	Progressive multifocal leukoencephalopathy
JCV	Polyomavirus JC
PCR	Polymerase chain reaction
CSF	Cerebrospinal fluid
MRI	Magnetic resonance imaging
CID	Combined immunodeficiencies
CVID	Common variable immunodeficiency
HSCT	Hematopoietic stem cell transplantation

Introduction

Progressive multifocal leukoencephalopathy (PML) is a rare but severe demyelinating disease caused by the reactivation and access to the brain of the ubiquitous polyomavirus JC (JCV), which targets oligodendrocytes and to lesser extent astrocytes. Conditions associated with cellular immunodeficiency, such as human immunodeficiency virus (HIV) infection, hematological malignancies, organ transplantation, and immunosuppressive therapy with monoclonal antibodies such as natalizumab for multiple sclerosis or Crohn's disease can cause PML. Immunodeficiency leads to reactivation of the virus from its latent reservoir in the kidneys, lymphoid tissue, and bone marrow-derived cells, leading to infection and lytic replication in the central nervous system and PML [1]. The clinical outcome of patients with PML is dismal, with an inexorable progression toward death within months after the onset of symptoms [2]. There is no specific antiviral treatment, and the only efficient therapeutic approach remains the reconstitution of a systemic antiviral immune response. The underlying pathogenesis of PML remains unclear.

Primary immune deficiencies (PIDs) are rare inherited disorders resulting in impaired immune responses that may lead to increased susceptibility to infections, immune dysregulation with autoimmune disease and aberrant inflammatory responses, and malignancy [3]. Over 340 distinct genetic disorders affecting the innate and/or adaptive arms of the immune system have been identified to date but many PIDs remain of unknown origin [4]. Susceptibility to infection can be broad or restricted to one pathogen (e.g., herpes simplex encephalitis associated with impaired TLR3 signaling [5]). PML can complicate the course of several types of PIDs, mostly PIDs with combined immunodeficiency [6–14]. Four patients with PML and dominant gain-of-function mutation in signal transducer and activator of transcription 1 (STAT1) were also recently reported [6]. Precisely how STAT1 is involved in the JCV regulatory pathway is unknown, but the authors suggest that this might be secondary to enhanced expression of programmed cell death protein ligands 1 (PD-L1) detected in T cells from STAT1 GOF patients, rendering T cells anergic and leading to T cell exhaustion and dysfunction [6].

So far, no study has systematically detailed the clinical and radiological presentation of PML occurring in PIDs. Here, we report a series of 11 patients with PID who developed PML during the course of their disease, and provide a description of the clinical, immunological, imaging features, and outcome.

Methods

This retrospective observational study was performed on a cohort of patients with PIDs from the French National Reference Center for Primary Immune Deficiencies (CEREDIH, Paris, France). Patients who developed PML as a first manifestation or during the course of PID were included. PIDs were classified according to the recent classification from the Primary Immunodeficiency Expert Committee of the International Union of Immunological Societies [4]. For each patient, disease history including infectious and non-infectious complications, clinical features, and immunological investigations before and at onset of PML were collected.

Immunologic analysis of the T, B, and natural killer cell compartments was performed by means of flow cytometry with a FACScalibur (BD Biosciences, Le Pont de Claix, France) and mAbs against CD3, CD4, CD8, CD19, CD16, CD45RA, and CD45RO, as described elsewhere [15, 16]. Lymphocyte proliferation was determined in vitro based on the amount of tritiated thymidine incorporated into peripheral blood mononuclear cells, as described previously [15, 16], after stimulation with PHA or specific antigen after an appropriate immunization schedule. Each study was run in parallel with samples from healthy adult control subjects.

Diagnostic criteria of the consensus statement from the American Academy of Neurology Neuroinfectious Disease Section were used for PML diagnosis [2]. For all patients, physical examination, neuroimaging finding, cerebrospinal fluid (CSF) characteristics, treatment, and outcome were collected. All the cerebral magnetic resonance imaging (MRI) were reviewed by a radiologist experienced in infectious diseases. Extensive microbiological investigations to rule out bacterial, viral, fungal, and mycobacterial infections were done in all patients in blood and CSF. Evaluation of JCV viral load was performed in CSF at the virology laboratory (Cochin Hospital, Paris, France) using real-time polymerase chain reaction (PCR) which targets a highly conserved 114 base-pair region of the JCV large tumor (T-antigen) gene. This

quantitative PCR system uses the forward primer 5′-CTTT TTAGGTGGGGTAGAGTGTTG-3′, the reverse primer 5′-TCCTGGTGGAATACATTTAATGAGAAG-3′, and the 6-carboxyfluorescein (FAM)-labeled probe 5′-CATG GCAAAACAGGTCT-3′.

Patients were classified as definite PML (compatible clinical features and imaging findings, CSF PCR for JCV positive), probable (compatible clinical features or imaging findings, CSF PCR for JCV positive), and possible (compatible clinical features and imaging findings, CSF PCR for JCV negative) [2]. When a brain biopsy was performed, the diagnosis of PML was based on the association of suggestive histopathological features (demyelination, "bizarre" astrocytes, oligodendrocytes containing nuclear inclusion bodies) and detection of JCV DNA by in situ hybridization [2].

This retrospective data collection was conducted according to the Helsinki Declaration and informed consent was obtained from the patients or their relatives.

Results

PID Characteristics

Eleven patients developed PML during PID evolution. PID features are summarized in Table 1. PIDs were characterized by a wide range of syndromic or genetically defined defects. Six patients had combined immunodeficiencies (CID) including one *MST1* deficiency, one *DOCK8* deficiency, one *CD40 ligand* deficiency, one *PRKDC* deficiency, and two CID without known genetic defect. Three patients were diagnosed with combined immunodeficiencies with syndromic features including one Wiskott-Aldrich syndrome, one cartilage-hair hypoplasia, and one immunodeficiency with centromeric instability and facial anomalies (ICF syndrome). Two patients had common variable immunodeficiency (CVID) without known genetic defect.

All patients but one (patient 9) had a previous history of infections (Table 1), mostly recurrent upper or lower respiratory tract infections ($n = 10$), but also *Herpesviridae* reactivations with clinical manifestations (herpes simplex virus ($n = 2$), varicella zoster virus ($n = 3$), cytomegalovirus ($n = 1$)). One patient (patient 1) had chronic symptomatic Epstein-Barr virus (EBV) replication treated by repeated courses of rituximab. Patient 4 developed several opportunistic infections before PML onset, including sinus and laryngeal aspergillosis, cryptosporidiosis, and *Pneumocystis jirovecii* pneumonia. Four patients had only recurrent upper and lower respiratory tract infections before PML development. Nine patients were receiving immunoglobulin replacement therapy. Concerning patient 9, a diagnostic of PID was established because all alternative secondary causes (HIV infection, hematological malignancies, or immunosuppressive therapy) of PML were ruled out and immunological abnormalities (i.e., lymphopenia and hypogammaglobulinemia) persisted many years after PML onset (see below).

Seven patients had autoimmune and/or inflammatory manifestations before PML onset, including autoimmune cytopenia ($n = 6$), granulomatous disease ($n = 4$), and polyarthritis ($n = 2$) (Table 1). Two patients had a regenerative nodular hyperplasia of the liver. Three patients developed malignancies during the evolution of PID and prior to PML: EBV-associated Hodgkin's lymphoma in patient 1, diffuse large B cell lymphoma in patient 8, and human papillomavirus-associated vulvar epidermoid carcinoma in patient 3. One patient (patient 10) had a chronic lymphoid interstitial pneumonia and hepatosplenic polyclonal lymphoproliferation treated by steroids and rituximab.

Table 2 shows the patients' immunologic features at PML diagnosis. In four patients, immunologic investigations were performed after immunosuppressive treatment (median 7.5, range 1–14 months) (Tables 1 and 3). Immunologic investigations showed severe T cell lymphopenia in nine cases (median 504, range 41–1392 $CD3^+$ cells/μL); this primarily involving $CD4^+$ lymphocytes (median 265, range 50–344 $CD4^+$ cells/μL), with a significant decrease in naïve T cell numbers (< 5% of the $CD45RA^+$/ $CD4^+$ cells; data not shown). All but one patient (patient 3) had profound hypogammaglobulinemia. A reduced or absent T lymphocyte proliferation upon stimulation with both mitogens and antigens was found in the five patients in whom the assay was performed.

PML Presentation

Ten patients had definite PML and one (patient 3) had possible PML. PML features are summarized in Table 3. Median age at PML onset was 23 years (range 15–64 years). PML revealed PID in one case (patient 9) whereas it complicated its evolution in the others with a median interval from PID diagnosis of 18 years (range 0–26 years). Median delay between first neurological symptoms and PML diagnosis was 2 months (range 0.25–4 months). Six patients had received prolonged immunosuppressive therapy in the year before the onset of PML (range 1 month–1 year), including prolonged oral steroid therapy in three cases, rituximab in four cases, and anti-TNF-α therapy (infliximab) and azathioprine in one case each. One patient (patient 8) was treated for diffuse large B cell lymphoma of the kidney by polychemotherapy including rituximab (R-CHOP) 5 months before PML onset, followed by allogeneic hematopoietic stem cell transplantation (HSCT). She was diagnosed with PML 1 month after HSCT but retrospective re-evaluation of pre-transplant cerebral imaging showed frontal hypodense lesion suggestive of pre-existing PML.

Cerebral MRI was abnormal in all cases. The main MRI features were large (> 3 cm), multiple (mean $n = 8$), bilateral,

Table 1 PID features before PML onset

	Sex	Type of PID (age at diagnosis) [genetic]	Infections (age at first infection)	Autoimmunity and/or inflammatory complications (age at onset)	Treatment	Lymphoproliferations/ malignancies (age at onset)	Treatment	Other
P1	M	MST1 deficiency (11) [*STK4* A117* HMZ]	URTI, LRTI EBV, VZV, molluscum (2)	Eczema (2)	None	Hodgkin lymphoma (5)	Polychemotherapy Radiotherapy	No
P2	M	Wiskott-Aldrich syndrome (3) [not available]	URTI, LRTI HSV, CMV, VZV, *Aspergillus* (1)	Eczema Autoimmune cytopenia (15)	Steroids Rituximab Azathioprin	None	NA	No
P3	F	DOCK8 deficiency (5) [*DOCK8* 2 HTZ large deletion]	URTI, LRTI HPV, *S. aureus* (4)	None	NA	Vulvar epidermoid carcinoma (20)	Surgery	No
P4	M	CD40 ligand deficiency (11) [not available]	URTI, LRTI HSV, *Aspergillus P. jiroveci*, *C. parvum* (6)	Arthritis Autoimmune neutropenia (30)	NSAI G-CSF	None	NA	RNH
P5	M	CID of unknown origin (14)	URTI (8)	Immune thrombopenia Pulmonary granulomatosis (9)	Steroids, IVIg	Splenomegaly	None	No
P6	F	Cartilage-hair hypoplasia (2) [*RMRP* C63T/A70G]	URTI, LRTI (1)	AIHA Granulomatous disease (16)	Steroids, IVIg Anti-TNF mAb	None	NA	No
P7	F	CVID of unknown origin (38)	URTI, LRTI (32)	Liver granulomatosis (58)	Budesonide	None	NA	RNH
P8	F	PRKDC deficiency (3) [*DNA-PKcs* delG2113/L3062R]	URTI, LRTI *Aspergillus* (4)	Polyarthritis Immune thrombopenia (10)	Methotrexate Splenectomy	DLBCL (22)	Polychemotherapy	No
P9	M	CID of unknown origin (29)	None	None	NA	None	NA	No
P10	F	CVID of unknown origin (53)	URTI, LRTI (40)	Immune thrombopenia Granulomatous disease (40)	Splenectomy Rituximab	Polyclonal lymphoproliferation (60)	Steroids Rituximab	No
P11	F	ICF syndrome (25) [centromeric instability on chromosome 16]	URTI, LRTI, VZV (2)	None	NA	None	NA	No

PID primary immunodeficiency, *CID* combined immunodeficiency, *CVID* common variable immunodeficiency, *HMZ* homozygous, *HTZ* heterozygous, *URTI* upper respiratory tract infections, *LRTI* lower respiratory tract infections, *EBV* Epstein-Barr virus, *CMV* cytomegalovirus, *VZV* varicella zoster virus, *HSV* herpes simplex virus, *HPV* human papillomavirus; *P. jirovecii Pneumocystis jirovecii*, *C. parvum Cryptosporidium parvum*, *NSAI* non-steroidal anti-inflammatory, *IVIg* intravenous immunoglobulin, *DLBCL* diffuse large B cell lymphoma, *RNH* regenerative nodular hyperplasia, *NA* not appropriate

Table 2 Immunological features at PML onset

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Absolute lymphocyte count/mm^3 (1000–4000)	700	1000	460	354	600	598	1600	598	750	1482	1365
CD3$^+$ cells/mm^3 (1000–2200)	504	880	184	163	486	41	1392	413	618	797	1225
CD4$^+$ cells/mm^3 (530–1300)	189	310	106	50	180	37	304	265	331	329	344
CD8$^+$ cells/mm^3 (330–920)	168	450	92	106	306	5	1008	141	233	466	868
CD19$^+$ cells/mm^3 (110–570)	4*	40*	207	92	12	18	176	1	39	1*	112
NK cells/mm^3 (70–480)	189	80	60	ND	84	539	80	175	45	594	15
IgG (g/L) (7–15)	20.8**	10.06**	16	5.58**	10**	7.14**	12**	7.5**	4.8	9.9**	8.91**
IgA (g/L) (0.8–3.5)	2.22	3.35	7.5	0.07	< 0.06	0.46	< 0.06	< 0.06	0.58	< 0.06	0.32
IgM (g/L) (0.6–2.6)	1,11	0.63	2.62	0.71	< 0.04	0.21	< 0.04	< 0.04	0.10	0.17	< 0.04

In brackets are age-matched normal values for lymphocyte counts and immunoglobulin levels (as established by the performing laboratory)

PML progressive multifocal leukoencephalopathy, *ND* not done, *NA* not appropriate, *NK* natural killer

*Patients treated by rituximab few months before immunologic investigations

**Immunoglobulin substitution

hypointense in T1 and hyperintense in T2-weighted areas with blurred limits, mainly sub-cortical, and located in the fronto-parieto-temporal white matter (Fig. 1). Involvement of basal ganglia was seen in six patients (Fig. 1a). Involvement of corpus callosum and posterior fossa was seen in three and five patients respectively. Peripheral punctiform contrast enhancement at diagnosis was noted in five patients (Fig. 1d). Hyperintense signal on diffusion-weighted imaging was observed in seven patients. Hemorrhages were seen in two patients but were not located in cerebral lesions and were suggestive of hypertensive hemorrhage. No mass effect was observed even when large lesions were present.

Lumbar puncture was performed in all patients. Increased cerebrospinal fluid (CSF) protein level (> 0.4 g/L) was noted in a single case whereas cell count was normal in all patients. PCR for JCV DNA in CSF was positive in 9/11 patients. Brain biopsy was required in one case (patient 9, Fig. 2) and showed typical lesions of PML with demyelinization lesion, atypical astrocytes, small amount of perivascular lymphocytes, atypical oligodendrocytes in periphery of lesions, and positive detection of JCV DNA by in situ hybridization (JCV PCR was not done on biopsy). In the last case (patient 3), diagnosis was established on the combination of compatible clinical and imaging features.

Treatment and Outcome

Eight patients received a treatment for PML, including cidofovir ($n = 5$), interleukin-7 ($n = 3$), interleukin-2 ($n = 2$), HSCT ($n = 2$), alpha interferon ($n = 1$), mirtazapine ($n = 1$), leflunomide ($n = 1$), and high-dose IVIg ($n = 1$). Treatment efficiency and outcome are summarized in Table 4. Cidofovir led to partial and transient clinical and MRI improvement with motor recovery and decrease in demyelinating lesions in two cases (patients 9 and 11) but failed in three others. Interleukin-7 showed partial clinical efficiency and MRI improvement in one case (patient 2, continued therapy was impossible because the drug was no longer available) but failed in two others (patients 5 and 10). HSCT led to rapid neurological degradation in both cases. No significant benefit was observed with the other treatments. All patients but one eventually died after a median of 8 months (range 0.25–36 months) following PML diagnosis. Patient 9 was still alive 10 years after PML diagnosis with sequelae hemiparesis.

Discussion

The reported prevalence of anti-JCV antibodies in adults varies from 39 to 91% depending on the assay methodology and population studied, indicating that a significant proportion of the population has been exposed to the virus [17–19]. However, the prevalence of PML in the general population has been estimated at 4.4 cases per 100,000 individuals [6, 17]. Primary infection with JCV is asymptomatic and occurs early in childhood, via oro-pharyngeal route from virus-contaminated material, possibly excreted virus in the urine [1]. The virus traffics to the bone marrow and kidneys in infected lymphocytes, where it can persist lifelong. PML neurotropic JCV strains harbor rearrangements in the genome non-coding regulatory region (NCCR) and sometimes mutations in the capsid VP1 coding sequence. When and how the virus gets access to the brain remains unknown. Profound immune deficiency and change in immune cell trafficking are considered as the main risk factors of developing PML. However, other host factors such as genetic susceptibility [20] may also play a role in PML pathogenesis [1].

Table 3 PML features

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11
Classification	Definite	Definite	Possible	Definite	Definite	Definite	Definite	Definite	Definite	Definite	Definite
Age at onset	18 years	18 years	15 years	35 years	23 years	18 years	64 years	22 years	29 years	61 years	24 years
Time after PID diagnosis (years)	17	15	10	24	9	18	26	22	0	8	20
Immunosuppressive therapy before onset/delay	Rituximab/1 month	Steroids, rituximab, azathioprine/9-months	No	No	No	Steroids, anti-TNF mAb/6 months	No	R-CHOP/5 months ASCT/1 month	No	Steroids, rituximab/14-months	No
Clinical symptoms	Paresthesia, motor deficit	Motor deficit	Paresthesia, cerebellar syndrome	Motor deficit, visual trouble	Epileptic crisis	Headache, tremor, ataxia	Motor deficit, memory disorders	Coma	Motor deficit, dysphonia, swallowing disorders	Frontal syndrome, confusion	Ataxia, comportemental trouble
Cerebral MRI abnormalities											
Lesions characteristics	Bilateral, large, multiple	Bilateral, large, multiple	Unique	Bilateral, small, multiple	Bilateral, small, multiple	Bilateral, large, multiple	Bilateral, large, multiple	Bilateral, large, multiple	Bilateral, large, multiple	Bilateral, large, multiple	Bilateral, large, multiple
Location	Fronto-parieto-occipital, basal ganglia, brainstem	Fronto-parietal, temporo-occipital, basal ganglia, brainstem	Cerebellum, brainstem	Frontro-parietal, temporo-occipital, corpus collosum, cerebellum	Fronto-parietal, temporal, basal ganglia	Fronto-temporal, basal ganglia, cerebellum, brainstem	Fronto-parietal, temporal	Fronto-temporal, basal ganglia	Fronto-parietal, basal ganglia	Frontal, corpus collosum	Fronto-parietal, temporo-occipital, corpus collosum
Contrast-enhancement	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	No
CSF characteristics											
Biochemistry	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Hyperproteinorachia	Normal	Normal	Normal
Cellular count	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
JCV PCR positive	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Brain biopsy	No	No	No	No	No	No	No	No	Yes	No	No

PML progressive multifocal leukoencephalopathy, *PID* primary immunodeficiency, *MRI* magnetic resonance imaging, *CSF* cerebrospinal fluid, *JCV* JC virus

While the humoral immune response has not been shown to control JCV infection, several observations point to a vital role of the cellular immune response for the control of the virus [1]. In AIDS, the incidence of PML was estimated at 3.3/100,000 patient-years before the introduction of HAART whereas it is now estimated at 1.3/100,000 patient-years and the risk of infection is correlated with $CD4^+$ T cell level [2, 21]. Moreover, a number of cases of PML have been reported in idiopathic $CD4^+$ T lymphopenia [7–9]. Consistent with these data, a majority of patients in our study had a profound T cell lymphopenia. However, the specific immune alterations leading to PML are unknown. Study of monogenic immune deficiencies complicated by PML may help to understand the pathways involved in infection development. PML may complicate the course of several types of PIDs, mostly PIDs characterized by combined B and T cell impairment. To our knowledge, including the present series, 24 cases of molecularly defined PIDs who developed PML have been reported in literature [6, 10–14]: *STAT1* GOF mutation ($n = 4$), Wiskott-Aldrich syndrome ($n = 4$), DOCK8 deficiency ($n = 3$), CD40 ligand deficiency ($n = 2$), ICF syndrome ($n = 2$), MST1 deficiency ($n = 1$), cartilage-hair hypoplasia ($n = 1$), PRKDC deficiency ($n = 1$), adenosine deaminase deficiency ($n = 1$), purine nucleoside phosphorylase deficiency ($n = 1$), RAG1 deficiency ($n = 1$), X-linked agammaglobulinemia ($n = 1$), MAGT1 deficiency ($n = 1$), and NFKB1 deficiency ($n = 1$). In this study, patients classified as having B cell CVID and without previous opportunistic infections also present clinical features suggestive of T cell impairment (i.e., autoimmune and inflammatory manifestations, $CD4^+$ T cell lymphopenia). Many of these patients developed PML many years after PID presentation, suggesting a possible specific immune exhaustion toward the JCV which might trigger the disease.

In the present study, half of the patients received immunosuppressive therapy in the year preceding the onset of PML, including prolonged steroid therapy, rituximab, anti-TNF-α therapy (infliximab), and azathioprine. Immunosuppressive treatments are frequently used to treat autoimmune, inflammatory, or proliferative complications of PIDs [3, 22, 23]. Natalizumab is a humanized monoclonal antibody directed to 휀4휁1 integrins that blocks traffic across the blood-brain barrier that blocks adhesion and transmigration of activated lymphocytes through the blood-brain barrier. It is used for the treatment of relapsing-remitting forms of multiple sclerosis and Crohn's disease and is one of the biological therapies that carries the highest risk of PML with an incidence of 1/100–1/1000 [18, 24, 25]. Rituximab has been associated with an incidence rate of 289/100,000 patient-years in patients with lymphoma, exceeding the rate observed in patients with HIV infection or B cell chronic lymphocytic leukemia (incidence of 5/1000), traditionally considered at highest risk of PML [25, 26]. To a lesser extent, this association was also found in patients treated for autoimmune rheumatological diseases

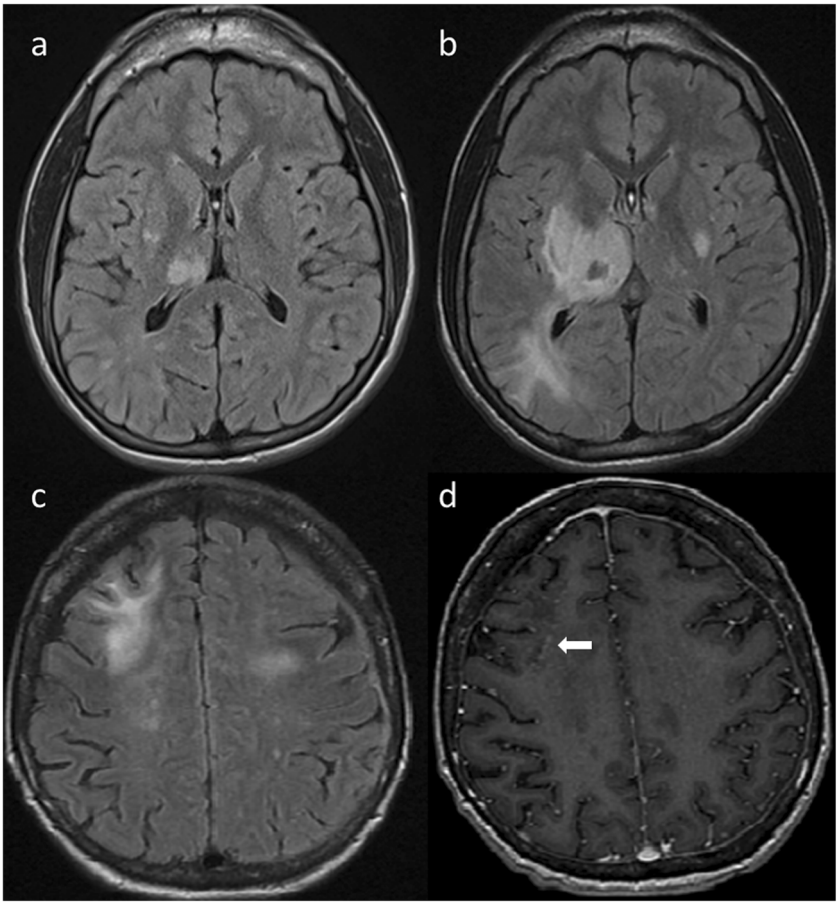

Fig. 1 Brain magnetic resonance imaging (MRI) findings in progressive multifocal leukoencephalopathy complicating primary immunodeficiencies. **a**, **b** Axial T2 FLAIR-weighted MR images from the same patient. **a** Initial MRI shows hypersignals of the right thalamus, right lentiform nucleus, and right parietal white matter. **b** Progression shows controlateral lesion and increase in size of the lesions. **c** Axial T2 FLAIR-weighted MR image showing hypersignals of bilateral white matter with involvement of the subcortical white matter of the right frontal lobe. **d** Axial contrast-enhanced T1-weighted MR image of the same patient demonstrates punctiform peripheral enhancement of the lesion (arrow)

[27] but a recent post-marketing study demonstrated that the occurrence of PML is very rare in this condition [28]. In PIDs, a study of 33 patients with CVID-associated autoimmune cytopenias treated with rituximab showed that 24% of patients developed severe bacterial infections after treatment, especially in patients off immunoglobulin replacement therapy and/or in patients who underwent splenectomy, but no PML case was reported [22]. Similarly, infliximab, a humanized monoclonal antibody against TNF-α-inducing apoptosis in TNF-α-producing T cells, has not been associated with PML in large cohorts of patients with Crohn's diseases [29], sarcoidosis [30], or rheumatoid arthritis [27]. In our study, one case of PML was diagnosed 6 months after initiation of anti-TNF-α therapy for granulomatous inflammation secondary to cartilage-hair hypoplasia. Through the US Adverse Event Reporting System (AERS), Schmedt et al. reported all signals of PML during immunosuppressive drugs [31]. Among 635 cases of PML, 7 were suggested to be secondary to azathioprine. However, possible interactions between different immunosuppressants were not be studied in details. The PML risk needs to be carefully evaluated before considering immunosuppressive therapy in the treatment of patients with PIDs. In patients with multiple sclerosis, the risk of developing PML during natalizumab treatment is significantly lower among anti-JCV antibody-negative patients compared with those who are positive [18, 32]. Testing JCV-DNA in urine could be complementary to testing anti-JCV antibody in identifying natalizumab-treated patients at risk of PML [33], while virus detection in serum or blood does is not a predictive factor [34]. Because serological status is difficult to assess in patients with PIDs, especially those receiving immunoglobulin replacement therapy, detection of JC virus by PCR on urine may be considered before initiation of these treatments in PIDs.

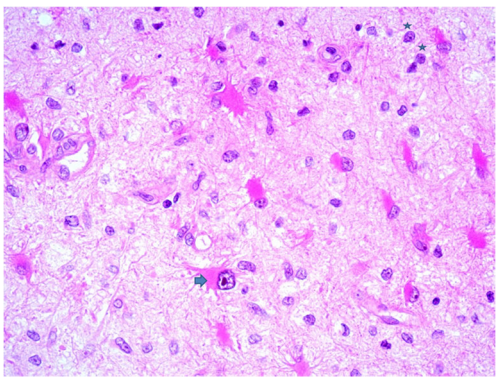

Fig. 2 Brain biopsy shows atypical astrocytes (arrowhead) and atypical oligodendrocytes in periphery of lesions (stars). Hemalun, phloxine, safran (H.P.S) coloration, × 40 original magnification

Table 4 PML treatment and outcome

	Treatment (dosing, duration)	Clinico-radiological efficacy	Death	Time of survival after PML diagnosis
P1	Cidofovir (5 mg/kg/week, 4 weeks)	No	Yes	4 months
	Alpha interferon (80 μg/week, 12 weeks)	Clinical stabilization		
P2	Interleukin-7 (10 μg/kg/week, 13 months)	Clinical and MRI improvement	Yes	15 months
		JCV PCR negativation		
P3	None	NA	Yes	12 months
P4	Cidofovir (5 mg/kg/week, 12 weeks)	No	Yes	4 months
	HSCT	No		
P5	Interleukin-7 (10 μg/kg/week, 4 weeks)	No	Yes	8 months
P6	Cidofovir (5 mg/kg/week, 4 weeks)	No clinical effect, MRI improvement	Yes	13 months
	Mirtazapine (unknown)	No		
	Leflunomide (unknown)	No		
	High-dose IVIg (unknown)	No		
	HSCT	No		
P7	None	NA	Yes	3 months
P8	None	NA	Yes	6 days
P9	Cidofovir (5 mg/kg/week, 11 months)	Clinical and MRI improvement	No	NA
	Interleukin-2 (4.5 MUI/6 weeks, 34 months)	Immunological improvement		
P10	Interleukin-7 (10 μg/kg/week, 5 weeks)	No	Yes	6 months
P11	Cidofovir (5 mg/kg/week, 26 months)	Clinical and MRI improvement	Yes	36 months
	Interleukin-2 (4.5 MUI/3 weeks, 12 weeks)	No		

MRI magnetic resonance imaging, *IVIg* intravenous immunoglobulin, *HSCT* allogenic hematopoietic stem cell transplantation, *NA* not appropriate

Diagnosis of PML may be challenging in PIDs because of a number of differential diagnosis for neurological involvement due to other infections, cerebral granulomatosis, or lymphoproliferation. In HIV patients with PML, cerebral MRI typically shows multifocal white matter lesion hypointense on T1 and hyperintense on T2-weighted and T2 FLAIR sequences [35]. Involvement of the parieto-occipital white matter, corpus callosum, and posterior fossa is commonly seen and there is usually no mass effect or enhancement. In our study, MRI pattern of PID-associated PML was more closely similar to PML seen in natalizumab-treated patients, with more frequent large lesions involving subcortical frontal regions (especially basal ganglia) and with frequent contrast enhancement [35, 36]. Similar to PML in patients with HIV or treated with natalizumab, very few had an abnormal elevated CSF protein and cell count was normal in all cases. The main value of CSF was demonstrating the presence of JCV by PCR [2, 37]. However, despite the high sensitivity of the PCR assay, a negative PCR does not rule out PML and in one case a brain biopsy was required.

Despite the introduction of HAART, the prognosis of PML is dismal with a mortality rate still near of 50% in HIV-infected patients. In patients with multiple sclerosis who develop PML, mortality is lower but severe morbidity is seen in survivors [1]. In this study, all patients but one died after a median of 8 months following PML diagnosis. However, one patient treated by cidofovir then interleukin-2 was still alive 10 years after PML onset with neurological sequelae. There is currently no established treatment for PML. A number of therapeutic options (such as cytarabine, acyclovir, cidofovir, chlorpromazine, mirtazapine, beta interferon, or mefloquine) have been evaluated but none has shown significant efficacy [35]. In PIDs, in absence of effective specific treatment, reconstitution of a systemic antiviral immune response remains the most efficient therapeutic approach. Adoptive T lymphocyte therapy with JCV-specific cytotoxic T lymphocytes showed efficiency in a patient with PML complicating HSCT [38]. Because they stimulate T cells, interleukin-2 [39] and interleukin-7 [40, 41] have been used with promising but contrasting results [42]. In this study, IL-2 and IL-7 were used in two and three cases respectively but showed clinical efficiency in only one. Both patients in the present series who underwent HSCT while presenting signs of PML rapidly died of the progression of infection. Because time to immune reconstitution is not compatible with evolution of infection, HSCT should therefore not be proposed as a specific treatment of PML. No immune reconstitution inflammatory syndrome was observed with both treatments.

In summary, PML is a rare but fatal complication of PIDs, affecting mostly patients with combined B and T cell impairment, even in the absence of previous opportunistic infections. PML tends to occur after the use of immunosuppressive

therapy, warranting careful evaluation and close neurological surveillance if such treatment is needed. Immunosuppressive therapy in patients with PID needs to be carefully weighed in the face of the increased risk of infection and particularly the possibility of developing PML in this population. Study of monogenic immune deficiencies developing PML will help to better understand specific pathways involved in development of this infection.

Compliance with Ethical Standards

This retrospective data collection was conducted according to the Helsinki Declaration and informed consent was obtained from the patients or their relatives.

Conflict of Interest The authors declare that they have no conflict of interest.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Ferenczy MW, Marshall LJ, Nelson CDS, Atwood WJ, Nath A, Khalili K, et al. Molecular biology, epidemiology, and pathogenesis of progressive multifocal leukoencephalopathy, the JC virus-induced demyelinating disease of the human brain. Clin Microbiol Rev. 2012;25:471–506.
2. Berger JR, Aksamit AJ, Clifford DB, Davis L, Koralnik IJ, Sejvar JJ, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology. 2013;80:1430–8.
3. Fischer A, Provot J, Jais J-P, Alcais A, Mahlaoui N, Members of the CEREDIH French PID study group. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol. 2017;140:1388–1393.e8.
4. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova J-L, Chatila T, et al. International Union of Immunological Societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. J Clin Immunol. 2018;38:96–128.
5. Pérez de Diego R, Sancho-Shimizu V, Lorenzo L, Puel A, Plancoulaine S, Picard C, et al. Human TRAF3 adaptor molecule deficiency leads to impaired Toll-like receptor 3 response and susceptibility to herpes simplex encephalitis. Immunity. 2010;33:400–11.
6. Zerbe CS, Marciano BE, Katial RK, Santos CB, Adamo N, Hsu AP, et al. Progressive multifocal leukoencephalopathy in primary immune deficiencies: Stat1 gain of function and review of the literature. Clin Infect Dis Off Publ Infect Dis Soc Am. 2016;62:986–94.
7. Haider S, Nafziger D, Gutierrez JA, Brar I, Mateo N, Fogle J. Progressive multifocal leukoencephalopathy and idiopathic CD4+ lymphocytopenia: a case report and review of reported cases. Clin Infect Dis Off Publ Infect Dis Soc Am. 2000;31:E20–2.
8. Rueger MA, Miletic H, Dorries K, Wyen C, Eggers C, Deckert M, et al. Long-term remission in progressive multifocal leukoencephalopathy caused by idiopathic CD4+ T lymphocytopenia: a case report. Clin Infect Dis Off Publ Infect Dis Soc Am. 2006;42:e53–6.
9. Patel A, Patel J, Ikwuagwu J. Treatment of progressive multifocal leukoencephalopathy and idiopathic CD4+ lymphocytopenia. J Antimicrob Chemother. 2010;65:2489–92.
10. Al Shekaili L, Sheikh F, Al Gazlan S, Al Dhekri H, Al Mousa H, Al Ghonaium A, et al. Novel mutation in DOCK8-HIES with severe phenotype and successful transplantation. Clin Immunol Orlando Fla. 2017;178:39–44.
11. Aschermann Z, Gomori E, Kovacs GG, Pal E, Simon G, Komoly S, et al. X-linked hyper-IgM syndrome associated with a rapid course of multifocal leukoencephalopathy. Arch Neurol. 2007;64:273–6.
12. Dhalla F, Murray S, Sadler R, Chaigne-Delalande B, Sadaoka T, Soilleux E, et al. Identification of a novel mutation in MAGT1 and progressive multifocal leucoencephalopathy in a 58-year-old man with XMEN disease. J Clin Immunol. 2015;35:112–8.
13. Schröder C, Baerlecken NT, Pannicke U, Dörk T, Witte T, Jacobs R, et al. Evaluation of RAG1 mutations in an adult with combined immunodeficiency and progressive multifocal leukoencephalopathy. Clin Immunol Orlando Fla. 2017;179:1–7.
14. Maffucci P, Filion CA, Boisson B, Itan Y, Shang L, Casanova J-L, et al. Genetic diagnosis using whole exome sequencing in common variable immunodeficiency. Front Immunol. 2016;7:220.
15. de Villartay J-P, Lim A, Al-Mousa H, Dupont S, Déchanet-Merville J, Coumau-Gatbois E, et al. A novel immunodeficiency associated with hypomorphic RAG1 mutations and CMV infection. J Clin Invest. 2005;115:3291–9.
16. Morelon E, Dautry-Varsat A, Le Deist F, Hacein-Bay S, Fischer A, de Saint Basile G. T-lymphocyte differentiation and proliferation in the absence of the cytoplasmic tail of the common cytokine receptor gamma c chain in a severe combined immune deficiency X1 patient. Blood. 1996;88:1708–17.
17. Bozic C, Subramanyam M, Richman S, Plavina T, Zhang A, Ticho B. Anti-JC virus (JCV) antibody prevalence in the JCV epidemiology in MS (JEMS) trial. Eur J Neurol. 2014;21:299–304.
18. Bloomgren G, Richman S, Hotermans C, Subramanyam M, Goelz S, Natarajan A, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. N Engl J Med. 2012;366:1870–80.
19. Amend KL, Turnbull B, Foskett N, Napalkov P, Kurth T, Seeger J. Incidence of progressive multifocal leukoencephalopathy in patients without HIV. Neurology. 2010;75:1326–32.
20. Power C, Gladden JG, Halliday W, Del Bigio MR, Nath A, Ni W, et al. AIDS- and non-AIDS-related PML association with distinct p53 polymorphism. Neurology. 2000;54:743–6.
21. Engsig FN, Hansen A-BE, Omland LH, Kronborg G, Gerstoft J, Laursen AL, et al. Incidence, clinical presentation, and outcome of progressive multifocal leukoencephalopathy in HIV-infected patients during the highly active antiretroviral therapy era: a nationwide cohort study. J Infect Dis. 2009;199:77–83.
22. Gobert D, Bussel JB, Cunningham-Rundles C, Galicier L, Dechartres A, Berezne A, et al. Efficacy and safety of rituximab in common variable immunodeficiency-associated immune cytopenias: a retrospective multicentre study on 33 patients. Br J Haematol. 2011;155:498–508.
23. Moshous D, Meyts I, Fraitag S, Janssen CEI, Debré M, Suarez F, et al. Granulomatous inflammation in cartilage-hair hypoplasia: risks and benefits of anti-TNF-α mAbs. J Allergy Clin Immunol. 2011;128:847–53.
24. Berger JR. Classifying PML risk with disease modifying therapies. Mult Scler Relat Disord. 2017;12:59–63.
25. Tuccori M, Focosi D, Blandizzi C, Del Tacca M, Petrini M. Re: rituximab maintenance for the treatment of patients with follicular lymphoma: systematic review and meta-analysis of randomized trials. J Natl Cancer Inst. 2009;101:1288–9 author reply 1289-1290.
26. Carson KR, Evens AM, Richey EA, Habermann TM, Focosi D, Seymour JF, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases

from the Research on Adverse Drug Events and Reports project. Blood. 2009;113:4834–40.
27. Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy associated with immunosuppressive therapy in rheumatic diseases: evolving role of biologic therapies. Arthritis Rheum. 2012;64:3043–51.
28. Berger JR, Malik V, Lacey S, Brunetta P, Lehane PB. Progressive multifocal leukoencephalopathy in rituximab-treated rheumatic diseases: a rare event. J Neuro-Oncol. 2018;24:323–31.
29. Lavagna A, Bergallo M, Daperno M, Sostegni R, Costa C, Leto R, et al. Infliximab and the risk of latent viruses reactivation in active Crohn's disease. Inflamm Bowel Dis. 2007;13:896–902.
30. Jamilloux Y, Cohen-Aubart F, Chapelon-Abric C, Maucort-Boulch D, Marquet A, Pérard L, et al. Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: a multicenter study of 132 patients. Semin Arthritis Rheum. 2017;47:288–94.
31. Schmedt N, Andersohn F, Garbe E. Signals of progressive multifocal leukoencephalopathy for immunosuppressants: a disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System (AERS). Pharmacoepidemiol Drug Saf. 2012;21:1216–20.
32. McGuigan C, Craner M, Guadagno J, Kapoor R, Mazibrada G, Molyneux P, et al. Stratification and monitoring of natalizumab-associated progressive multifocal leukoencephalopathy risk: recommendations from an expert group. J Neurol Neurosurg Psychiatry. 2016;87:117–25.
33. Laroni A, Giacomazzi CG, Grimaldi L, Gallo P, Sormani MP, Bertolotto A, et al. Urinary JCV-DNA testing during natalizumab treatment may increase accuracy of PML risk stratification. J Neuroimmune Pharmacol Off J Soc NeuroImmune Pharmacol. 2012;7:665–72.
34. Viscidi RP, Khanna N, Tan CS, Li X, Jacobson L, Clifford DB, et al. JC virus antibody and viremia as predictors of progressive multifocal leukoencephalopathy in human immunodeficiency virus-1-infected individuals. Clin Infect Dis Off Publ Infect Dis Soc Am. 2011;53:711–5.
35. Sahraian MA, Radue E-W, Eshaghi A, Besliu S, Minagar A. Progressive multifocal leukoencephalopathy: a review of the neuroimaging features and differential diagnosis. Eur J Neurol. 2012;19:1060–9.
36. Wattjes MP, Vennegoor A, Steenwijk MD, de Vos M, Killestein J, van Oosten BW, et al. MRI pattern in asymptomatic natalizumab-associated PML. J Neurol Neurosurg Psychiatry. 2015;86:793–8.
37. Clifford DB, De Luca A, DeLuca A, Simpson DM, Arendt G, Giovannoni G, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol. 2010;9:438–46.
38. Balduzzi A, Lucchini G, Hirsch HH, Basso S, Cioni M, Rovelli A, et al. Polyomavirus JC-targeted T-cell therapy for progressive multiple leukoencephalopathy in a hematopoietic cell transplantation recipient. Bone Marrow Transplant. 2011;46:987–92.
39. Kunschner L, Scott TF. Sustained recovery of progressive multifocal leukoencephalopathy after treatment with IL-2. Neurology. 2005;65:1510.
40. Alstadhaug KB, Croughs T, Henriksen S, Leboeuf C, Sereti I, Hirsch HH, et al. Treatment of progressive multifocal leukoencephalopathy with interleukin 7. JAMA Neurol. 2014;71:1030–5.
41. Gasnault J, de Goër de Herve M-G, Michot J-M, Hendel-Chavez H, Seta V, Mazet A-A, et al. Efficacy of recombinant human interleukin 7 in a patient with severe lymphopenia-related progressive multifocal leukoencephalopathy. Open Forum Infect Dis. 2014;1:ofu074.
42. Pavlovic D, Patera AC, Nyberg F, Gerber M, Liu M. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives. Ther Adv Neurol Disord. 2015;8:255–73.