Published in final edited form as:
Pediatr Infect Dis J. 2014 April ; 33(4): e99–105. doi:10.1097/INF.0000000000000237.

Progressive Multifocal Leukoencephalopathy in Pediatric Patients: Case Report and Literature Review

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a rare, demyelinating disease of the central nervous system caused by JC virus. Fewer than 30 cases have been reported in HIV-infected and non-infected children. We report the case of a 15 year-old girl with PML and AIDS who presented with nystagmus, dysarthria, and ataxia. Following combined antiretroviral therapy, she developed immune reconstitution inflammatory syndrome, which proved fatal.

Keywords

Progressive multifocal leukoencephalopathy (PML); JC virus; HIV; granule cell neuron; pediatric

CASE DESCRIPTION

A 15-year-old girl with a history of recurrent otitis media and bilateral herpes simplex virus keratitis presented with a six-week history of fatigue, 12 kg weight loss, right hand and leg

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Conflicts of interest
The authors have no additional financial relationships or conflicts of interest relevant to this article to disclose.

clumsiness, diplopia, dysarthria and gait instability. Although the patient's biological mother was HIV infected, the patient's HIV status was unknown to her adoptive family. Details regarding the biological mother's medical history, including HIV management, were unknown. Physical examination revealed an acneiform rash of the face, thrush, sustained nystagmus with up-, left- and rightward gaze, diplopia with rightward gaze, right lower face weakness, dysarthria, truncal ataxia, and a wide-based gait.

Laboratory tests revealed a white blood cell count of 2,580/mm^3 and absolute CD4 count of 5 cells/mm^3. Additional laboratory testing demonstrated a positive HIV-1 antibody and plasma viral load of 82,000 copies/mL. Cerebrospinal fluid was notable for protein of 30.3 mg/dL, glucose 51 mg/dL, white blood cell count 2 cells/mL, HIV-1 viral load 99,400 copies/mL, and JCV PCR 4,200 copies/mL. Cerebrospinal fluid gram stain, culture, CMV PCR, EBV PCR, HSV PCR, KOH, fungal culture, cryptococcal antigen, acid fast bacillus (AFB) stain, AFB culture, and toxoplasma PCR were negative. A brain MRI demonstrated patchy regions of T2 signal hyperintensity within the right cerebellar hemisphere, middle cerebellar peduncle, and diffusely within the pons and medulla (Figure 1*A*). Vascular ectasia of the supraclinoid internal carotid arteries was present bilaterally and consistent with a history of perinatal HIV infection.

Based on the radiographic findings and positive JCV CSF PCR, the patient was diagnosed with AIDS and progressive multifocal leukoencephalopathy (PML). Combination antiretroviral therapy (cART) was initiated with nevirapine, tenofovir/emtricitabine and raltegravir. Her antiretrovirals were chosen based on their favorable penetration into the central nervous system. Shortly after cART initiation, the patient developed worsening dysarthria, dysphagia, and aspiration of liquids and a repeat MRI demonstrated new and increased bilateral medullary lesions concerning for immune reconstitution inflammatory syndrome (IRIS). Based on the interval radiographic changes and neurologic worsening, she was started on high-dose methylprednisolone followed by a prednisone taper. The patient's neurologic status improved and she was discharged approximately one month following admission.

She was readmitted one week later for urinary incontinence, worsening dysarthria, new left hemiplegia, and inability to ambulate. A repeat MRI showed interval increase in T2-signal abnormalities of the brainstem and cerebellum. Given her significant clinical and radiographic progression, the patient was given a second course of methylprednisolone. Despite this, she had progressive weakness, inability to clear secretions, and developed generalized tonic-clonic seizures. Repeat MRI demonstrated new, diffuse supratentorial lesions and interval worsening of the infratentorial lesions (Figure 1*B, E, F*). She had worsening respiratory drive and a progressively diminished level of consciousness and died eight weeks following her initial presentation.

REVIEW

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system that results from infection with JC virus (JCV), a neurotropic polyomavirus whose only known reservoir is humans.[1] While well-described among HIV-infected adults,

PML has been rarely reported in immunosuppressed pediatric patients who are HIV-infected or have a primary immunodeficiency, cancer, or solid organ transplant.

Epidemiology

Epidemiologic seroprevalence surveys estimate that up to 86% of healthy adults have been exposed to JCV. One recent study demonstrated that JCV age-specific seroprevalence rises from about 16% in children 1-5 years of age to 34% by age 21-50 years.[1, 2] This increase in JCV seroprevalence over time may explain why PML is relatively uncommon among children. Once infected, latent virus persists within reservoirs including the bone marrow, tonsillar B-lymphocytes and proximal renal tubule cells.[3] Factors that determine whether the virus remains quiescent, reactivates, or progresses to cause PML are unknown.

PML has been reported largely among patients infected with HIV.[3] A retrospective review of 13 Pediatric AIDS Clinical Trials Group (PACTG) studies conducted before the advent of cART revealed a PML event rate of 0.06 per 100 person years, with affected children identified at a median age of 10.8 years and median CD4 count of 6 cells/mm.[4, 5] The rarity of PML among HIV-infected children was initially thought to be secondary to perinatally-infected children dying before they experienced primary JCV acquisition.[6] Concerns that improved outcomes and prolonged survival would result in an increased incidence of PML among HIV-infected children have not been borne out.[7]

We identified 19 reported cases of PML among HIV-infected children (Table 1).[6, 8-23] Of the 19 published reports, 12 patients acquired HIV via vertical maternal-to-child transmission, 4 via blood product transfusions, 1 from a contaminated needle, and 1 from an orthotopic liver transplant. The source of infection for one child was not reported. Twelve (63%) of the identified patients were male and the median age at PML diagnosis was 12 years (range 6-22 years). Only 3/19 (16%) of patients were newly-diagnosed with HIV at the time of PML presentation.[6, 12, 18] CD4 count was <500 cells/mm^3 in all but one patient. Viral load was reported in 5 cases and ranged from 11,800-292,000 copies/mL.

PML has also been described in 10 children with a history of solid organ transplant, malignancy, or primary immunodeficiency, including hyperimmunoglobulin E, hyperimmunoglobulin M, Wiskott-Aldrich, and severe combined immunodeficiency (Table 2).[24-33] PML presenting symptoms, radiographic findings, and histopathologic findings in these immunosuppressed children resembled those of HIV-infected children.

Clinical Presentation

Clinical manifestations of PML are variable and depend on the region of the central nervous system affected. Symptoms are likely the result of demyelination that occurs due to lytic oligodendrocyte infection. The most commonly reported signs among adults include paresis, speech abnormalities, gait disturbances, ataxia and cranial nerve palsies.[34, 35] Our review revealed similar findings in children, including hemiparesis, ataxia, and dysarthria. Seizures occur in 18% of PML adult patients and were noted in 4/29 (14%) of the pediatric cases.[15, 20, 28, 31, 36]

Neuroimaging

MRI is the most widely utilized radiographic modality for the evaluation of PML. Typical radiographic features include a single or multiple non-space-occupying, T2-hyperintense, T1-hypointense lesions without associated edema. These lesions commonly involve the frontal and parieto-occipital subcortical white matter.[37] Involvement tends to be asymmetric with relative sparing of the periventricular white matter. PML lesions have also been described in gray matter structures and the spinal cord.[38, 39] Enhancement of PML lesions in patients not undergoing immune reconstitution was once thought to be atypical, although this assumption has been challenged by more recent reports.[9, 40] As in adults, lesions in the 25 pediatric PML cases with radiographic information predominantly involved white matter and most (84%) demonstrated no enhancement with gadolinium contrast. Posterior fossa and brainstem involvement was common. In the present case, areas of enhancement were noted in the right basal ganglia, medulla, and cerebellum; histopathology from these areas was consistent with PML. Cortical enhancement noted shortly before her death, however, was not consistent with PML on histopathology (Figure 1*E*, *F*).

Pathology

Characteristic histopathologic features of PML in children, as in adults, include foci of demyelination involving the white matter and gray-white junction, lesions with abundant lipid-laden macrophages and bizarre astrocytes, and enlarged oligodendrocytes with intranuclear inclusions. The case patient's pathology included multiple foci of demyelination in the brainstem and cerebellum, featuring oligodendrocytes with large, ground-glass nuclei and large, bizarre astrocytes with prominent nucleoli (Figure 1*D*, Figure 2*A*, *B*). In addition, there were intraparenchymal infiltrates of CD163+ macrophages and CD8+ T lymphocytes.

In contrast to published pediatric cases, JCV immunoreactivity was visualized within both oligodendrocytes and cerebellar granule cell neurons in our case patient (SV40 antibody staining, Figure 2*C*, *D*). Further staining of the granule cell layer for JCV T Ag and VP1 protein expression was notable for a predominance of granule cell neurons expressing T Ag only, consistent with early or restricted infection, with rare VP1-expressing cells indicating productive infection. These findings are consistent with earlier observations that although JCV infection was initially thought to be limited to glial cells, restrictive granule cell neuron infection may also be important in pathogenesis.[41]

Laboratory Diagnostics

A definitive diagnosis of PML can be established by detection of JCV DNA in the CSF or viral proteins on brain biopsy. In adults with PML the reported sensitivity of JCV DNA CSF PCR is 58%, with an estimated specificity of 100%.[42] Given the relatively low sensitivity, cases with characteristic clinical and neurologic manifestations can be categorized as having 'possible PML' even in the absence of positive molecular diagnostics.[43] The majority of reported pediatric cases had a positive JCV CSF PCR (17/29, 59%).

CSF white cell count, protein, and glucose are usually normal to slightly elevated in patients with PML.[34, 44] Among the reported cases in HIV-infected children, none had pleocytosis and all had a normal glucose (48-92 mg/dL) and a normal to slightly elevated protein (12-76

mg/dL).[6, 10, 11, 13-16, 19, 20, 23, 34] Among case reports in children without HIV, the CSF profiles, including cell count, glucose, and protein, were also within normal limits.[26, 28, 30-32]

Treatment

Immune system restoration is the mainstay of PML management. Although cART does not have direct anti-JCV activity, survival among HIV-infected adults with PML has increased from 10% in the pre-cART era to 50% with cART.[45, 46] The effects of antiretroviral drugs on PML outcomes in children are unknown; only 7/19 (37%) of published cases initiated cART at the time of their PML diagnosis.[11-16, 18]

Additional treatment modalities have been used for the management of PML. Inconsistent improvements in clinical progression have been reported in adults treated with cidofovir, cytarabine, or alpha-interferon therapy.[47, 48] Among the HIV-infected pediatric patients, two were treated with cidofovir and had improvement in their neurologic status.[12, 13] Two HIV-uninfected children were treated with cidofovir. One patient had complete resolution of neurologic symptoms, although this patient's immunosuppression was also reduced as part of their PML management.[25, 27]

Immune Reconstitution Inflammatory Syndrome

In a subset of patients with PML, inflammation and an apparent increase in JCV-mediated tissue destruction follow the suppression of HIV infection with cART. This PML-associated IRIS is a severe, often fatal, complication. Histologically, the syndrome is marked by infiltration of brain parenchyma by CD8+ lymphocytes, as was noted in the case patient.[40]

PML-IRIS occurs in 19-31% of adult patients with PML, most often within 1 week to 26 months of cART initiation.[49-51] Among the 19 reported cases of PML in HIV-infected children, 3 (16%) had clinical courses concerning for PML-IRIS, with the onset of neurologic symptoms 12-28 days after starting cART.[14, 16, 18]

Steroids have been used for PML-IRIS, especially in cases of rapid clinical deterioration or when neuroimaging demonstrates inflammation. In one series of adults who received steroids, 58% had good neurologic recovery; those who survived received steroids earlier in their course and had contrast enhancement of their PML lesions on MRI.[51] All 4 reported cases of HIV-infected children with suspected PML-IRIS received steroids; two had a protracted neurologic course and two died.

Prognosis

The prognosis of PML in children is poor. Though the prognosis for HIV-infected patients with PML has improved with the introduction of cART, the lack of an agent with activity against JCV has hampered efforts to improve overall survival. Among pediatric PML cases, only 5/16 (31%) HIV-infected patients and 2/10 (20%) patients without HIV survived.[11, 13-16, 25, 28] The remainder died within one year of PML diagnosis, most by 2-6 months. The majority of survivors had long-term neurologic deficits including residual hemiparesis and cerebellar dysfunction.

Several factors, including JCV CSF viral load, CD4 count >100 cells/mm^3, contrast enhancement on radiographic imaging, evidence of neurologic function recovery, and the presence of JCV-specific cytotoxic T-cells, have been suggested to predict survival among HIV-infected adults with PML.[52-57] Specific predictors of mortality in children remain to be elucidated.

Acknowledgments

source of funding: This work was supported in part by the National Institute of Allergy and Infectious Diseases (NIAID) T32 AI 007433 (L.R.); Agency for Healthcare Research and Quality (AHRQ) T32 HS 019485-01; National Institute of Child Health and Human Development (NICHD) T32 HD 055148-02 (L.R.), R56 NS 041198, R01 NS 047029, R01 NS 074995 and K24 NS 060950 (I.J.K).

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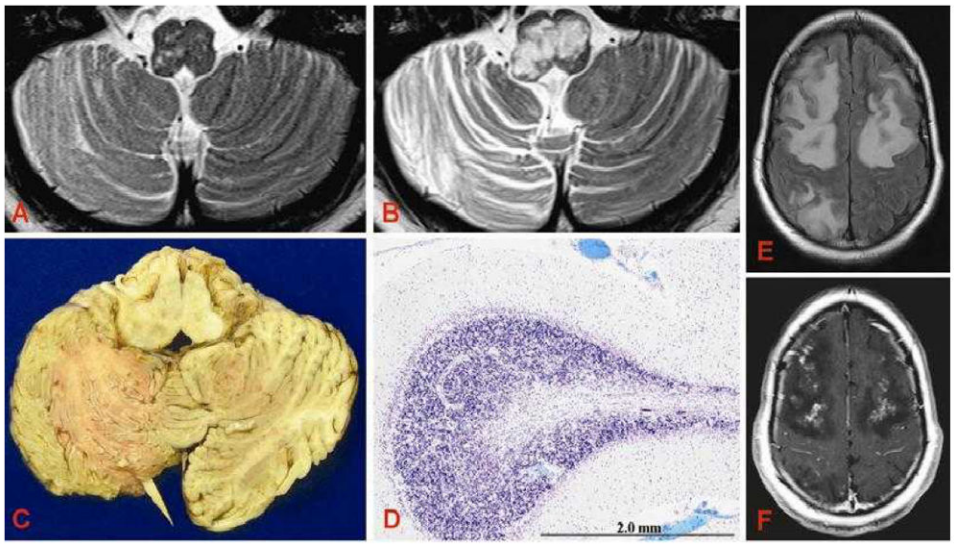

Figure 1. Radiographic, pathologic, and histologic characteristics of PML

A, T2-weighted MRI images captured at the time of presentation and *B*, six weeks later (three days prior to death). *C*, Marked volume loss in the right cerebellar folia and distortion of the medulla are likewise seen at the gross level. *D*, Luxol fast blue (LFB) staining demonstrates marked destruction and demyelination of the cerebellar white matter. *E*, FLAIR and *F*, gadolinium-enhanced T1 MRI three days prior to death demonstrates extensive subcortical and deep white matter edema and contrast enhancement.

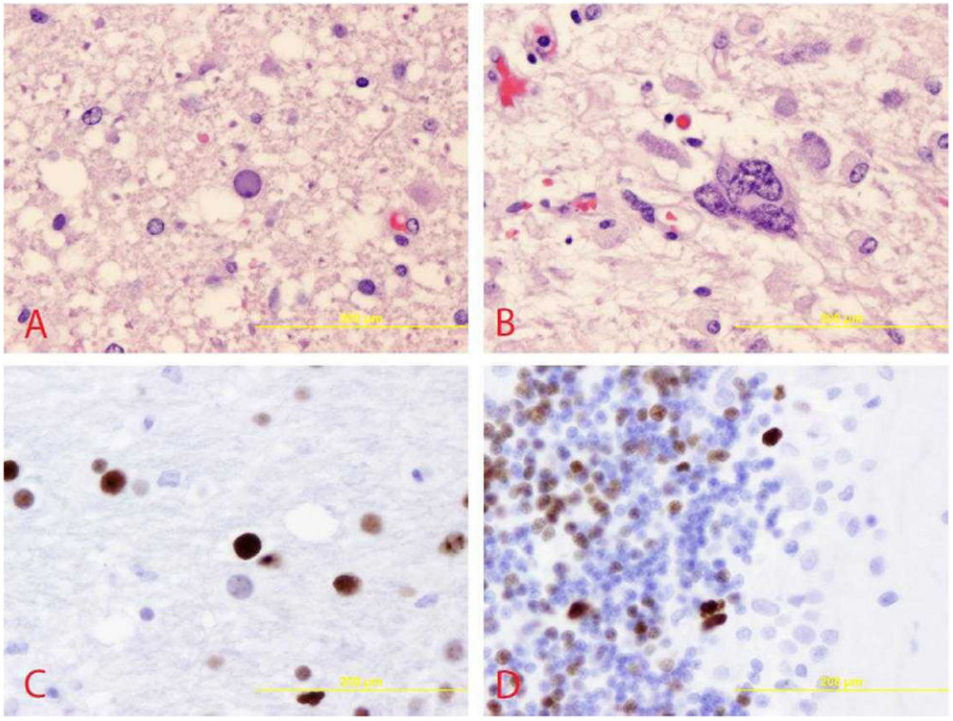

Figure 2. Immunohistologic characteristics of PML

A, Infected and diseased oligodendrocytes showing enlarged, ground-glass appearing nuclei, mostly found at the edges of demyelination (pons, 400X). *B*, Bizarre, multi-nucleated astrocytes often found within demyelinated lesions (pons, 400X). *C*, Immunohistochemistry staining, highlighting JCV-infected oligodendrocytes (pons, 400X). *D*, and JCV-infected granule cell neurons of the cerebellum (400X).

Table 1

Characteristics of Previously Reported Pediatric Progressive Multifocal Leukoencephalopathy (PML) Cases in HIV-Infected Children

Case	Reference	Age at PML diagnosis, years	Sex	Initial presentation	CD4 count (cells/mm^3) Viral load (copies/mL)	Initial neuroradiology	PML diagnosis	Treatment	IRIS	Outcome
Index		15	F	Dysarthria, fatigue, dysphagia, hemiparesis	CD4=5 VL=82,000	MRI: T2 hyperintensities of right cerebellum, midbrain, pons, medulla; vascular ectasia supraclinoid carotid arteries	CSF JCV PCR + Typical histopathology Immunohistochemistry Granule cell neuron infection	cART, steroids	Yes	Died
1	6	7	M	Left upper and lower extremity weakness, drooling, difficulty eating	CD4=390 VL=NR	MRI: Bilateral white matter hyperintensities of right subcortical/ periventricular region	Typical histopathology In situ hybridization +	AZT	No	Died
2	8	13	F	Numbness of tongue and chin, sialorrhea, dysarthria, dysphagia, muteness	CD4=7 VL=NR	MRI: Prominent basal ganglia lesions, scattered white matter lesions	CSF JCV PCR + Typical histopathology In situ hybridization +	AZT, interferon	No	Died
3	8	10	M	Right facial palsy, right hemiparesis, aphasia	NR	MRI: Left frontal lobe lesion	Typical histopathology In situ hybridization +	None	No	Died
4	22	8	M	Right-sided hemiparesis, aphasia	NR	CT: Tortuous, dilated internal carotid, left middle/anterior cerebral arteries	Typical histopathology	AZT	No	Died
5	9	10	M	NR	NR	NR	NR	NR	No	NR
6	9	12	F	NR	NR	NR	NR	NR	No	NR
7	19	13	F	Blurred vision, headache, drooling, dysphagia, dysarthria	CD4=7 VL=NR	MRI: Lesions of the corona radiata, centrum semiovale, basal ganglia, right periatrial white matter	CSF JCV PCR+ Typical histopathology In situ hybridization +	AZT, interferon	No	Died
8	21	12	M	NR	NR	NR	Typical histopathology	None	No	Died
9	10	7	M	Decreased activity, slurred speech, ataxia	CD4=0	MRI: Prolonged T1/T2 relaxation in right	CSF JCV PCR+ Typical histopathology In situ hybridization+	ddC, steroids, radiation therapy	No	Died

Case	Reference	Age at PML diagnosis, years	Sex	Initial presentation	CD4 count (cells/mm^3) Viral load (copies/mL)	Initial neuroradiology	PML diagnosis	Treatment	IRIS	Outcome
					VL=NR	cerebellar white matter, peduncle, pons				
10	[23]	11	M	Fatigue, headache, unsteadiness, left- cerebellar symptoms	NR	MRI: Focal high T2 signal lesion in cerebellum/brainstem	Typical histopathology	AZT	No	Died
11	[11]	12	M	Left upper extremity weakness, left low extremity pain	CD4=9.5 VL=76,000	MRI: White matter lesions right frontal/ parietal/occipital lobes	CSF JCV PCR +	cART	No	Hemiparesis
12	[12]	13	F	Headache, right hemiparesis	CD4=17 VL=292,000	MRI: Hyperintense T2 white matter lesions right cerebellar/pons	CSF JCV PCR +	cART, cidofovir	No	Died
13	[13]	16.5	M	Dysarthria, right facial palsy, drooling	CD4=36 VL=29,100	MRI: Diffuse confluent T2 areas of high signal in the bilateral corona radiata	CSF JCV PCR +	cART, cidofovir	No	Cerebellar dysfunction
14	[14]	12	M	Dizziness, headache, left arm weakness, left cerebellar dysfunction, left facial weakness	CD4=49 VL=Undetectable	MRI: Hyperintense lesions left cerebellar hemisphere, pons, medulla	CSF JCV PCR +	cART, steroids	Yes	Mild cerebellar dysfunction
15	[15]	8.5	F	Change in mental status, spasticity of all four limbs, dystonia, seizures	CD4=320 VL=NR	MRI: Asymmetrical subcortical, right frontoparietal, left occipitoparietal/basal ganglia lesions	Radiographic	cART	No	Dystonia
16	[20]	6	F	Short term memory loss, myoclonic and generalized seizures	NR	CT: Mineralization of left basal ganglia	CSF JCV PCR – Radiographic	None	No	LTFU
17	[16]	22	F	Speech difficulty, right facial drooping, right-sided weakness	CD4=10 VL=11,800	MRI: White matter lesions, left ventricular compression of left hemisphere	CSF JCV PCR +	cART, steroids	Yes	Progressive improvement
18	[17]	15.5	M	Dizziness, diplopia, fatigue, depression, ataxia	NR	MRI: Lesion of right cerebellar hemisphere with slight mass effect, right cerebellar peduncle	CSF JCV PCR+ Typical histopathology	cART	No	Died

Pediatr Infect Dis J. Author manuscript; available in PMC 2015 April 01.

Case	Reference	Age at PML diagnosis, years	Sex	Initial presentation	CD4 count (cells/mm^3) Viral load (copies/mL)	Initial neuroradiology	PML diagnosis	Treatment	IRIS	Outcome
19	[18]	9	M	Right-sided facial palsy, right-sided hemiplegia	CD4=4 VL=185,976	CT: Hypodense lesions left frontal lobe with lateral ventricle effacement	CSF JCV PCR+	cART, steroids	Yes	Died

PML, progressive multifocal leukoencephalopathy;
VL, viral load;
CSF, cerebrospinal fluid;
JCV, JC virus;
cART, combination antiretroviral therapy;
IRIS, immune reconstitution inflammatory syndrome;
NR, not reported;
AZT, zidovudine;
ddC, zalcitabine;
LTFU, lost to follow-up

Pediatr Infect Dis J. Author manuscript; available in PMC 2015 April 01.

Table 2

Characteristics of Previously Reported Pediatric Progressive Multifocal Leukoencephalopathy (PML) Cases in non-HIV-Infected Children

Case	Reference	Age at PML diagnosis, years	Sex	Initial presentation	Underlying Condition	Initial neuroradiology	PML diagnosis	Treatment	Outcome
Index		15	F	Dysarthria, fatigue, dysphagia, hemiparesis	HIV Infection	MRI: T2 hyperintensities of right cerebellum, midbrain, pons, medulla; vascular ectasia supraclinoid carotid arteries	CSF JCV PCR + Typical histopathology Immunohistochemistry Granule cell neuron infection	cART, steroids	Died
1	24	15	M	Nausea, headache, impaired ocular movements, anarthria, aphasia	6mo post-BMT for WAS; immunosuppression not reported	MRI: High T2 signal in right occipital lobe, cerebellum, pons, right corona radiate, left thalamus, and basal ganglia	CSF JCV PCR + Typical histopathology	Acyclovir, ribavirin, IFN-α	Died
2	25	11	M	Vomiting, fever, somnolence	3.5y post-deceased donor renal transplant on MMF/prednisolone/ rapamycin immunosuppression; CVID	MRI: Enhancing lesions of right thalamic region, brain stem, parietal medullary layer	Serum JCV PCR + Radiographic	Cidofovir MMF discontinued	Complete resolution
3	26	6	M	Right-sided hemiparesis, memory deficits, decreased volume/fluency of speech, hyperreflexia	Hyper-IgM	MRI: Multifocal white matter lesions involving the left cerebral hemisphere and bilateral thalami	CSF JCV PCR + Brain biopsy JCV PCR + Typical histopathology	Cytarabine	Died
4	27	8	M	Cognitive slowness, left facial muscle weakness	HIES	MRI: Hyperintense lesions of right frontal white matter, internal capsule, and right thalamus	CSF JCV PCR + Typical histopathology Immunohistochemistry	Cidofovir	Died
5	28	6	M	Lethargy, left-sided hemiparesis, seizures	ALL (in remission for 2.5y)	MRI: Contrast enhancement with loss of cortical sulci due to cortical edema	Brain biopsy JCV PCR + Typical histopathology	Amantadine	Hemiparesis, pale optic disks, no light perception
6	29	7	M	Left facial twitching and weakness, impaired vision	ALL (in remission for 2y)	MRI: Hyperintense lesions of gray-white interface involving the right frontal, parietal and occipital regions	Radiographic	NR	Died
7	30	15	M	Right-sided weakness, behavior changes, decreased speech output	WAS	MRI: Multiple high-intensity lesions in brain stem and cerebrum, including left thalamus and basal ganglia	PBL JCV PCR + Typical histopathology Immunohistochemistry	Dexamethasone	Died
8	31	9	M	Seizure, cognitive deficits, progressive spastic paraparesis	PNP Deficiency	MRI: T2-hyperintense lesions in the white matter of both hemispheres, particularly affecting the parietal regions	CSF JCV PCR+	IVIG Exchange transfusion Trimethoprim-sulfamethoxazole	Died
9	32	16	M	Mental status changes, decreased communication, nystagmus	3y post cadaveric renal transplant on MMF/prednisone immunosuppression	MRI: T2-hyperintense lesions of midbrain, basal ganglia, cerebral white matter with more lesions on right	CSF JCV PCR + Brain biopsy JCV PCR + Typical histopathology Viral particles on EM	NR	Died
10	33	11	M	Right-sided hemiparesis, irritability, aphasia, apraxia, inability to walk	SCID	NR	Typical histopathology Immunohistochemistry	NR	Died

PML, progressive multifocal leukoencephalopathy;
CSF, cerebrospinal fluid;
JCV, JC virus;
cART, combination antiretroviral therapy;
BMT, bone marrow transplant;
IFN-α, interferon-alpha;
SCID, severe combined immunodeficiency;

NR, not reported;
WAS, Wiskott-Aldrich syndrome;
MMF, mycophenolate mofetil;
CVID, common variable immunodeficiency;
Hyper-IgM, hyperimmunoglobulin M syndrome;
HIES, hyperimmunoglobulin E recurrent infection syndrome;
ALL, acute lymphoblastic leukemia;
PBL, peripheral blood lymphocytes;
PNP, purine nucleoside phosphorylase;
IVIG, intravenous immunoglobulin;
EM, electron microscopy