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REVIEW ARTICLE

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Progressive multifocal leukoencephalopathy in transplant recipients

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Abstract Progressive multifocal leukoencephalopathy (PML) is a demyelinating infection caused by the JC virus. It is an emerging disease in transplant recipients; however, it remains poorly defined. Twenty-four cases of PML reported in the literature in transplant recipients were reviewed. Of the 24 cases, nine occurred in renal, six in bone marrow, four in liver, three in heart and two in lung transplant recipients. Median time to onset was 17 months; 71% occurred within 24 months of transplantation. PML tended to occur later in the kidney recipients ($P=0.04$). Seventy-five percent had subacute presentation; hemiparesis (50%), apathy (46%) and confusion (38%) were the most frequently presented features. Treatment included reduction of immunosuppression and chemotherapy, mainly cidofovir. Death occurred within 2.5 months of the onset of symptoms in 17 patients (71%). PML is a unique entity that should be considered in any transplant recipient with neurological symptoms. The outcome is usually fatal, although regression has been reported.

Keywords Progressive multifocal leukoencephalopathy · Transplantation · JC virus · Immunosuppression · Central nervous system

Introduction

Progressive multifocal leucoencephalopathy (PML) is a rare demyelinating disease of the central nervous system caused by a neurotropic papovavirus named the JC virus (JCV). By far the most common underlying immunosuppressive illness is AIDS, accounting for approximately 85% of PML cases currently seen in clinical practice [1]. PML was also reported in patients with lymphoma, leukaemia, systemic lupus erythematosus, and chronic inflammatory diseases such as sarcoid and tuberculosis [1, 2]. It has also been reported in transplant recipients, most probably due to their immunosuppressive treatment. The virus causes lysis of oligodendrocytes, resulting in microscopic foci of myelin breakdown that coalesce to produce increasingly larger lesions [2]. The virus also infects astrocytes, in which morphological features develop that are suggestive of neoplasia, including mitotic figures and multinucleated forms [2]. Although prolonged survival and clinical remission have been described, most affected patients die within months [1, 2]. PML may become more prevalent as the population of transplant recipients increases. High clinical

suspicion, however, is needed in order to diagnose this disease.

This article summarizes the clinical characteristics, pathology, and management of PML in transplant recipients on the basis of existing literature and published reports. Cases published in the literature in December 2003 were identified through a MEDLINE search by use of the keywords: transplantation; PML; central nervous system; JC virus. Additional cases were identified by manual review of the bibliographies of the original articles and review articles.

Patients were considered to have PML if the diagnosis was made by the authors reporting the case and no other aetiology could account for the disease on review of the case description or pathology.

Incidence and epidemiological characteristics

To date, no data exist about the incidence of PML in transplantation, as most of the reported literature *is* case reports. The overall incidence in AIDS patients is estimated to range from 4% to 7% [3], and over half of the deaths due to PML are associated with HIV infection [4, 5].

Of a total of 24 cases of PML reported in the literature in transplant recipients (Table 1), nine occurred in renal transplant recipients [6, 7, 8, 9, 10, 11, 12, 13, 14], six in bone marrow [15, 16, 17, 18, 19, 20], 4 in liver [21, 22, 23, 24], three in heart [25, 26, 27], and two in lung (single lung, one, double lung, one) transplant recipients [28, 29]; 13 were male (54%). Patients' ages ranged from 21 to 69 years (median 46 years); 46% (11/24) of the patients were younger than 45 years. Renal transplant recipients with PML were younger than all other patients (37 years vs 49 years, $P=0.06$). All of the solid-transplant recipients received immunosuppressive treatment. Eighty-three percent of the patients received corticosteroids, 72% azathioprine, 56% cyclosporine A, 17% FK-506 (tacrolimus) and 11% received mycophenolate mofetil (MMF).

Time of onset

The median time of onset of PML following transplantation was 17 months and ranged from 1 week to 132 months. Overall, 71% (17/24) of the cases of PML occurred within 24 months of transplantation. Renal transplant recipients seemed to develop these lesions later after transplantation than did other transplant recipients. The median time to onset was 30 months after transplantation in renal transplant recipients, 8 months in bone marrow transplant recipients, 15 months in liver, and 24 months in heart and lung transplant recipients. In three renal transplant patients (12.5% of the patients, 33.3% of the renal transplant patients) PML began more than 5 years after the transplantation. Compared with other transplant recipients, there was a trend towards a later occurrence of PML in renal transplant recipients (median 30 vs 11 months, $P=0.04$). A possible explanation for this difference could be the lesser degree of immunosuppression required in renal transplant recipients than in other transplant recipients.

Clinical features

The clinical presentation of PML in patients that had received transplants was characterized by a subacute course in 75% of the patients (18/24); in six patients (25%) who presented with agitation or focal neurological signs the course was more abrupt. The clinical features of the patients are summarized in Table 2. The most common presenting symptoms were mono- or hemiparesis (50%), apathy (46%) and confusion (38%). The symptoms worsened gradually over the course of days to weeks, and new neurological manifestations appeared, usually resulting from a spread of the lesion or from new lesions at remote sites.

In 50% (12) of the patients the picture was of focal motor neurological deficits. Usually, the weakness progressed, and 33% (four) of these patients developed tetraparesis with bilateral pyramidal signs.

Changes in mental status were common and occurred in most of the patients. Forty-six percent (11 of 24) demonstrated apathy and behavioural changes, and 38% (nine of 24) were confused and disorientated; 12.5% (three of 24) developed pseudobulbar changes. Frontal release signs were described in 12.5% (three) of the 24 patients, and speech disturbances were reported in 25% (six) of the 24.

Seizures were described in 21% (five) of the 24 patients. They usually occurred as the disease progressed, and most patients had focal motor seizures.

Visual symptoms occurred in 29% of the patients (seven of 24). Five of them developed homonymous hemianopsia. In three patients the visual disturbances were the presenting symptoms of the disease. The diagnosis was usually delayed due to diagnosis of cataracts (to which these patients are prone since they receive prolonged treatment with corticosteroids). However, their sight did not improve after cataract excision but continued to deteriorate, and a pattern of homonymous hemianopsia gradually appeared.

Sensory symptoms, ataxia, disco-ordination and memory impairment were described in 29% of the patients (seven of 24). Extrapyramidal signs were described in four patients (17%). Alexia, dyscalculia, Gerstmann's syndrome, incontinence, dizziness, apraxia and headache were described in single patients. Several patients

Table 1 Summary of 24 patients with progressive multifocal leukoencephalopathy following transplantation (*M* male, *F*female, *AZA* azathioprine, *BM* bone marrow, *CS* corticosteroids, *CsA* cyclosporine A, *FK 506* tacrolimus, *IFN* interferon, *IL-2* interleukin 2, *IS* immunosuppression, *ISH* in situ hybridization, *IVIG* intravenous immunoglobulin, *MMF* mycophenolate mofetil, *ND* no data, *PCR-CSF* polymerase chain reaction-cerebrospinal fluid, *Tx* transplantation)

Patient	Gender/age in years	Organ	Immuno-suppressant Tx	Onset after Tx (months)	Neurological features	Neuroimaging findings	Diagnosis	Treatment	Outcome	Interval onset to death (months)	Reference
1	M/34	Kidney	AZA; CS	30	Ataxia; confusion; apathy; headache	ND	Post-mortem	None	Died	2	[6]
2	M/34	Kidney	AZA; CS	13	Apathy; loss of memory; confusion; hemiparesis	Brain scan: normal	Post-mortem	None	Died	2.5	[7]
3	F/39	Kidney	AZA; CS	17	Visual; apathy; hemiplegia; dysarthria	Brain scan: normal	Post-mortem	None	Died	3.5	[8]
4	M/28	Kidney	CsA; CS	120	Ataxia; hemiparesis; dysarthria	CT: parieto-occipital enhancement	Biopsy	Cytosine arabinoside; Stop IS	Alive	–	[9]
5	F/66	Kidney	ND	5	Hemiparesis	CT: normal; MRI: multiple lesions	Biopsy + ISH	Lower IS; ganciclovir	Died	14	[10]
6	M/69	Kidney	CsA; CS	132	Headache; apathy; confusion	CT: brain atrophy; MRI: multiple lesions	MRI + PCR-CSF	None	Died	3	[11]
7	M/53	Kidney	AZA; CS	72	Confusion; ataxia	CT: no PML	Biopsy	None	Died	0.5	[12]
8	F/21	Kidney	AZA; CS	16	Hemiplegia; epilepsy	ND	Post-mortem	None	Died	5	[13]
9	M/28	Kidney	AZA; CS	39	Hemiplegia; seizure; apraxia	CT: Frontoparietal lesion	Biopsy	Lower IS	Alive	–	[14]
10	F/31	BM	None	17	Confusion	MRI: temporal lesion	Biopsy + ISH	Cytarabine	Alive	–	[15]
11	F/38	BM	IVIG	7	Acalculia; aphasia homonymous hemianopsia	MRI: white matter lesions	MRI + PCR-CSF	IL-2; IFN	Died	4	[16]
12	F/46	BM	IL-2	8	Vertigo; aphasia; hemiparesis	MRI: frontoparietal lesion	Biopsy + ISH	IL-2	Alive	–	[17]
13	F/44	BM	CsA, BMTx; T cell Ab	5	Dizziness; loss of memory; visual; hemiparesis; dyscalculia; apraxia; ataxia	CT: bilateral lesions; MRI: more lesions than shown on CT	Biopsy	Cytosine arabinoside; Stop IS	Died	2	[18]
14	M/43	BM	CsA, MTX; T cell Ab	17	Hemiparesis; dysphasia; dysarthria	CT: parietal lesion MRI: parietal white matter lesion	MRI	Cytosine arabinoside	Died	2	[19]

15	F/54	BM	IVIG	12	Loss of memory	CT: parietal lesion; MRI: bilateral white matter lesion	MRI	Cytosine arabinoside; IL-2	Alive	–	[20]
16	M/51	Liver	AZA; CsA; CS	1.5	Hemiparesis; seizure; apathy	CT: parietal lesion	Biopsy	Cytosine arabinoside; Stop IS	Died	4	[21]
17	F/53	Liver	AZA; CsA; CS	1.5	ND	None	Post-mortem	None	Died	18	[22]
18	F/55	Liver	CsA; CS	0.25	Blindness; hemiparesis	CT: bilateral diffuse lesions	Post-mortem + ISH	None	Died	ND	[23]
19	F/60	Liver	AZA; CsA; CS	11	Confusion; loss of memory; apathy	MRI: widespread white matter lesions	MRI + PCR-CSF	Cytosine arabinoside; Stop IS	Alive	–	[24]
20	M/59	Heart	AZA; CsA; CS	48	Visual loss; hemiparesis	MRI: bilateral lesions	Biopsy	None	Died	2	[25]
21	M/59	Heart	CsA; CS	24	Apathy; confusion	None	Post-mortem	None	Died	0.75	[26]
22	M/49	Heart	AZA; CsA; CS	57	Dizziness; ataxia	CT: internal capsule lesion	Post-mortem	None	Died	0.5	[27]
23	M/43	Lung	AZA; CsA; CS	15	Visual; seizure; ataxia; dysarthria	MRI: bilateral white matter lesions	PCR-CSF	Stop IS	Died	15	[28]
24	M/55	Lung	FK 506; MMF; CS	7	Hemiplegia; apathy; seizure; visual	CT: frontal hypodense lesion; MRI: bilateral lesions	Biopsy	Lower IS; cidofovir	Alive	–	[29]

Table 2 Spectrum of neurological manifestations of progressive multifocal leukoencephalopathy in 24 transplant recipients

Manifestation	Patients
Weakness	
Hemiparesis	12
Generalized	4
Apathy	11
Confusion	9
Impaired memory	7
Ataxia	7
Dysarthria	6
Aphasia	5
Apraxia	5
Visual loss	7
Homonymous hemianopsia	5
Blindness	1
Poor vision	1
Headache	2
Tremor	1
Seizure	5
Gerstmann's syndrome	1
Incontinence	1
Dizziness	1

had fever in the course of their disease; however, an infectious source was identified in all of the cases.

In one patient who died from another cause, the diagnosis of PML was made only at autopsy.

Laboratory studies

Results of cerebrospinal fluid (CSF) studies were reported in 15 patients (63%). The CSF content was normal in all patients, except for a mildly elevated protein level (up to 100 mg/dl) in four patients. Recently, polymerase chain reaction (PCR) of the CSF for the JCV was found to have a sensitivity of 72% to 93% and a specificity of 92% to 100% in HIV-positive persons [30]. Therefore, it is now accepted as a diagnostic test for PML [31]. In our study the test was done in only six patients and was positive in four [11, 16, 24, 28]. In one patient where there was immunofluorescence of the CSF to the JCV, a test for SV40 was done but was found to be negative.

Neuroimaging studies

Computed tomography (CT) scans in patients with PML characteristically reveal hypodense, non-enhancing lesions of the cerebral white matter [32]. The severity of the clinical findings is often greater than suggested by the extent of involvement on the CT scan. Magnetic resonance imaging (MRI) appears to be more sensitive than CT in detecting PML lesions [32, 33]. PML lesions typically appear as areas of increased signal intensity on proton-density and T2-weighted MR images (Fig. 1).

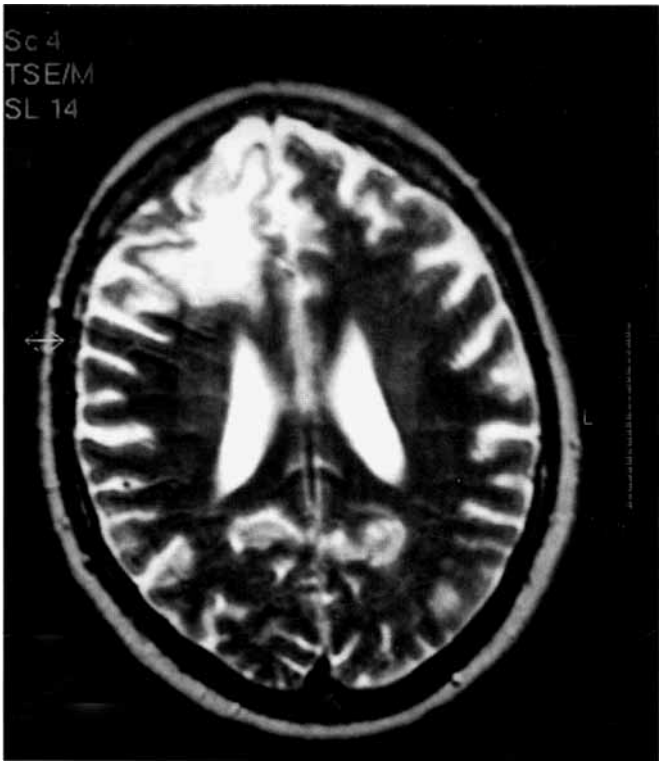

Fig. 1 MRI of the brain in a patient with PML demonstrated a right frontal white matter lesion

Fifty percent (12 of 24) of the patients underwent MRI; neuroimaging abnormalities were detectable in all. Parietal, occipital and temporal lobes were the most common sites of neuroimaging abnormalities in the posterior hemispheres. Neuroimaging abnormalities were usually located in the subcortical white matter but some had extended into the deeper white matter or the cortical ribbon. Coexistent haemorrhage was detected in one case. Other sites involved included cerebellum (two cases), pons, basal ganglia and corona radiata (one case, each). Lesions were non-enhancing in all cases, and mass effect was distinctly unusual (documented in one of 24 cases only).

One entity deserves particular mention while we are considering the differential diagnosis of PML in organ transplantation. The clinical and neuroimaging appearance of PML may mimic immunosuppression (cyclosporine or tacrolimus)-associated leukoencephalopathy [34]. Both often begin as asymmetric lesions in white matter with high signal intensity on T2-weighted MR images and low attenuation on CT. As in PML, contrast enhancement and mass effect are characteristically lacking. Immunosuppression-associated leukoencephalopathy, however, is an early occurring lesion, and the neuroimaging and clinical abnormalities are reversible on cessation or reduction of cyclosporine or tacrolimus [34].

Pathological findings

A definitive diagnosis of PML required identification of the characteristic pathological changes on brain biopsy. The fundamental pathological process of PML is destruction of oligodendrocytes, the myelin-producing cells of the central nervous system [35]. The areas of the brain most affected are the cerebral hemispheres, especially the parieto-occipital region, followed by the cerebellum and the brainstem. The spinal cord is usually spared. On gross examination of the brain, the cortex, meninges, and deep grey matter structures are normal. Myelin loss appears as grey foci in white matter and non-haemorrhagic softening of the white matter [32, 35]. Microscopically, PML is characterized by a triad of multifocal sites of demyelination with axon sparing, giant bizarre astrocytes with large pleomorphic nuclei and large hyperchromatic oligodendrocytes at the periphery of the lesions (Fig. 2). The oligodendrocytes contain large, round nuclei packed with viral particles. On electron microscopy, JCV particles appear in the nucleus of an infected oligodendrocyte (Fig. 3). Eighty-three percent (20 of 24) of the transplant recipients with PML underwent pathological examination; 50% (12 of 24) of the patients underwent brain biopsy and 33% (eight of 24) autopsy. In all cases the pathological examination showed the typical feature of PML. Foci of PML always involved cerebral white matter and only one case involved the cortical grey matter. PML was found in the cerebellum of seven patients, and brain stem lesions were noted in five patients. No case of spinal cord involvement was seen. White matter abnormalities ranged from myelin pallor and demyelination to frank necrosis. Almost all cases of PML demonstrated severe involvement of the grey–white matter junction. Nuclear inclusions in JCV-infected oligodendrocytes were found principally at the periphery of demyelinated areas, though they were also seen within regions of pallor or mild demyelination. The presence of *bizarre* or enlarged astrocytic nuclei was noted in demyelinated areas in all but two autopsies and in three of the biopsy

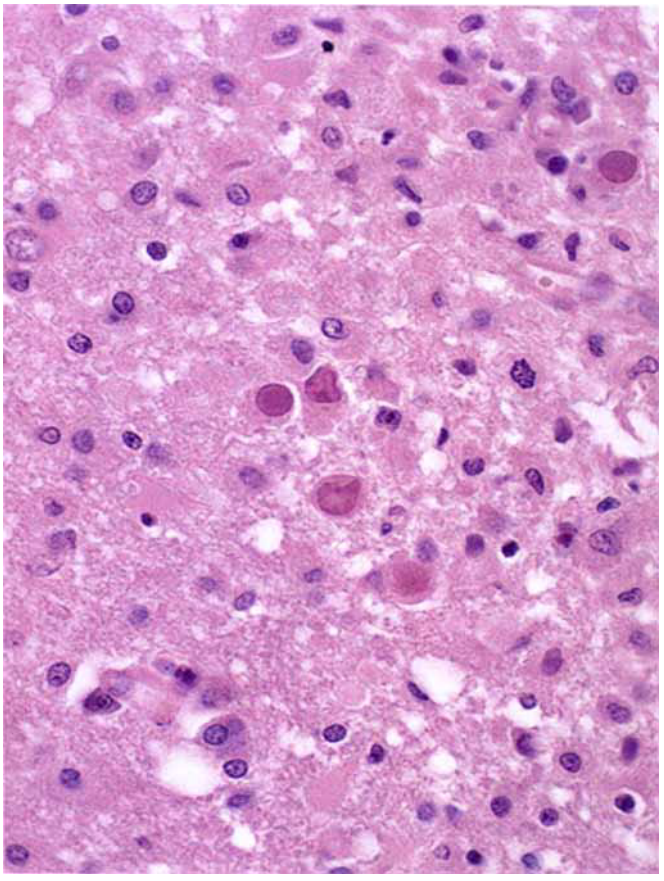

Fig. 2 Microscopic appearance of PML lesion with perivascular monocytes, astrocytosis with bizarre or enlarged astrocytes and central lipid-laden macrophages. At the periphery of the lesions are large "ballooned" oligodendrocytes infected with the JC virus that have enlarged dark-pink "ground glass" nuclei containing viral antigen. Hematoxylin-eosin, original magnification ×500)

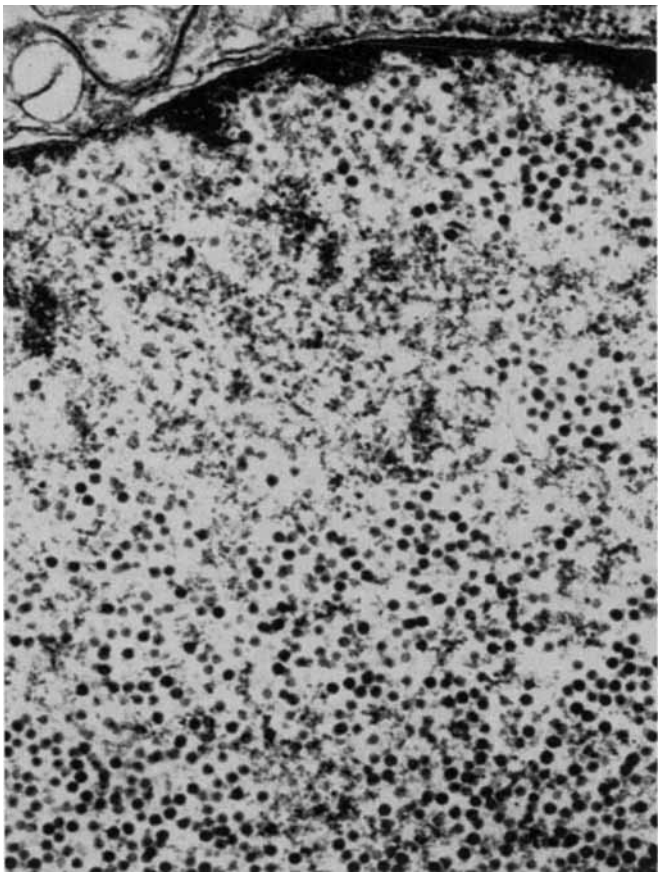

Fig. 3 Higher magnification of small, round, dark, JC viral particles appear in the nucleus of an infected oligodendrocyte (original magnification ×60,000)

specimens. Virus particles of the papova group were found in inclusion-bearing nuclei by immunohistochemical techniques in six cases—three biopsy and three autopsies. In situ hybridization (ISH) for JCV revealed that the number of infected oligodendrocytes was much higher than anticipated from the simple presence of inclusion-bearing oligodendrocytes in routine haematoxylin and eosin stained sections. PML was diagnosed in five patients by ISH of the pathology specimens. Electron microscopy (EM) showed intra-nuclear spherical and filamentous forms of virus particles in tissue from 11 patients, eight of 12 autopsies and three of eight biopsies.

Course and prognosis

Of the 24 patients, 71% (17) died, 53% of them (nine patients) directly from PML. The median duration of PML in these patients was 2.5 months (range 0.5–15 months), without significant differences for the patients that died directly from PML. Attempted therapy of the PML was tried unsuccessfully in five patients and included reduction of immunosuppressive therapy in three patients, cytosine arabinoside in four, and IL-2 and alpha-interferon, each in one patient. In all those patients the described course was relentlessly progressive, with multifocal neurological signs and deterioration of consciousness.

Only seven patients (29%) are reported to have survived. All but two of them, however, suffered from residual neurological damage. Median time to PML onset in these patients was 12 months and ranged between 7 and 120 months. Three of the patients underwent bone marrow transplantation (BMT), two renal transplantation, one liver, and one lung transplantation. Duration from PML onset ranged from 4 to 56 months. In all seven patients the immunosuppressive therapy was reduced to the minimum, and five of them received treatment for PML—cytarabine (three patients), IL-2 (one patient), and cidofovir (one patient). Cidofovir, a nucleoside analog, emerged recently as the most selective anti-polyomavirus agent [29, 36].

There were no specific clinical manifestations that differentiate these patients from those who died. All but two patients suffer from residual neurological damage, which includes hemiparesis, speech difficulties, dementia, partial incontinence, or myoclonic jerks. Improvement of their neurological symptoms, however, is described, with treatment and time.

Conclusions

PML comprises a unique entity characterized by subcortical white matter changes in the cerebral hemispheres. Lesions usually occur within 17 months of transplantation, with a tendency for a later onset in renal compared with other transplant recipients. Hemiparesis, apathy and confusion are the commonest initial complaints. MRI appears to be more sensitive than CT in detecting PML lesions. PCR of the CSF for JCV is now accepted as a diagnostic test for PML. A definitive diagnosis, however, requires brain biopsy. Treatment of transplant recipients with PML is largely supportive and directed towards minimizing immunosuppression. Cidofovir, a nucleoside analog, emerged recently as the most selective anti-polyomavirus agent that has been reported to stop progression in a few recipients. Death occurred within 2.5 months from the onset in 71% of the recipients. The clinical, neuroimaging, and neuropathological findings of PML in transplant recipients were similar to those of non-transplant-related PML, with some exceptions. Late onset was noted in the transplant recipient PML, fewer patients presented with visual loss and more lesions were noted in the cerebellum and in the brainstem. Early recognition of this central nervous system disease may be important, with new advances in therapy of this viral infection of the immunocompromised patient.

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