

LETTER TO THE EDITOR**To THE EDITOR****Unexpected Progressive Multifocal Leukoencephalopathy in a Hemodialysis Patient**

Keywords: Progressive multifocal leukoencephalopathy, PML, John Cunningham virus, JC virus, Hemodialysis, Chronic renal failure

Progressive multifocal leukoencephalopathy (PML) is a rare opportunistic infection of the central nervous system caused by John Cunningham virus (JCV), a polyomavirus (1). It primarily occurs in patients with immune deficiency such as malignancies, HIV infection, or immunosuppressive therapy (2). Reports of PML in patients without clear immunodeficiency are extremely rare (3). Here, we describe the case of an 87-year-old man with chronic renal failure on hemodialysis and no clear immune suppression who presented with progressive neurological decline, and post mortem studies led to the diagnosis of PML.

An 87-year-old male, with end-stage renal disease on hemodialysis and multiple vascular risk factors, presented with 2-week history of right arm weakness and dysarthria. Initial computed tomography (CT) scan of the head demonstrated no acute abnormality. Magnetic resonance imaging (MRI) of the brain (diffusion-weighted imaging (DWI) only) demonstrated a right cerebellar lesion which was interpreted as a subacute infarct (Figure 1A-C). Clopidogrel was added to his home antiplatelet (Aspirin), stroke workup was initiated, and he was transferred to stroke rehabilitation.

Four weeks later, he received a percutaneous gastric tube due to progressive dysphagia. His Holter monitor revealed new atrial fibrillation.

In less than a week, he was readmitted with progressive right-sided weakness, worsening dysphagia, and aspiration pneumonia. Despite treatment with moxifloxacin, he continued to have gradual neurological decline, and repeat MRI revealed that the previous area of high signal intensity in the right brachium pontis and cerebellum had progressed. New patchy areas of signal changes were seen in the left and central pons and cerebellum.

MRI of the brain with gadolinium was subsequently performed. The lesions were reported as being unusual in appearance for ischemic changes, with a differential diagnosis including osmotic demyelination and inflammatory or infectious etiologies. He was started on moxifloxacin 400 mg IV daily (the patient had documented allergies to penicillin and cephalosporins).

Lumbar puncture showed WBC: $1 \times 10^6/L$, RBC: $9 \times 10^6/L$, glucose: 7 mmol/L (H), protein: 0.61 g/L (H) (reference range: 0.15–0.45 g/L); cerebrospinal fluid (CSF) gram stain, cytology, and polymerase chain reaction (PCR) for CMV, EBV, HSV1/2 and VZV, were negative.

Antimicrobial therapy was discontinued. Repeat CT scan of the brain showed expansion of the abnormal signal. Empiric high-dose IV steroid therapy was initiated, but he had continued clinical deterioration. A brain biopsy was discussed, but the patient requested the transition to comfort care only. He died 77 days following his initial presentation, and a consented autopsy was performed.

Macroscopic examination of the brain showed subtle mottling of the base of the pons, middle cerebellar peduncles, and paramedian cerebellar white matter bilaterally (Figure 1D). Microscopically, there was extensive established demyelination in the pons, right middle cerebellar peduncle, and paramedian cerebellum bilaterally (Figure 1E). There were multiple small foci of active ongoing demyelination in the left middle cerebellar peduncle (Figure 1F), and in these areas, there were numerous enlarged oligodendrocyte nuclei containing amphophilic material (Figure 1G), characteristic of JCV infection. Frequent hypertrophic astrocytes with large pleomorphic nuclei (another characteristic feature of PML) and numerous debris-filled macrophages were present in areas of established demyelination. There was JCV-related cerebellar granule cell neuronopathy, which focally was severe with complete loss of internal granule cells (Figure 1H), while elsewhere in the cerebellar cortex there were multifocal groups of enlarged JCV-infected granule cells (Figure 1I). There was multifocal demyelination in the rostral medulla oblongata, but only small microscopic foci in the caudal medulla and midbrain, and no evidence of PML in supratentorial structures. Stored CSF was sent for JC virus PCR, which was positive.

In our review of the literature, we identified five cases of PML-reported patients with chronic renal failure, three on hemodialysis, without overt immune suppression (Table 1).

There are reports that patients with chronic renal disease, in the absence of kidney transplantation or immune suppression, are at higher risk of developing malignant tumors (4), suggesting that chronic renal failure may represent a state of subtle immune suppression. A study of 38 patients with end-stage renal disease demonstrated altered balance of T cell-associated immunity compared to controls, particularly with lowered naïve T cell percentage and increased percentage of Th17-producing effector memory cells and central memory T cells (5). The exact mechanism of JCV reactivation in chronic renal failure has not been established.

PML commonly affects white matter of the cerebral hemispheres, and isolated posterior fossa manifestations are uncommon (6), although cases have been described (7). JCV classically causes lytic infection of astrocytes and oligodendrocytes. Similar to our case, JCV may also infect cerebellar granule cell neurons (granule cell neuronopathy) leading to selective neuronal loss and gliosis (8).

Table 1: Reported cases of PML in patients with chronic renal failure

Reference	Age and sex	Details of renal insufficiency	HD	Duration of HD (years)	Initial presentation	CSF analysis	MRI findings	Pathological findings	Management	Outcome
Yoshifumi Arai et al., <i>Neuropathology</i> (2002) 22: 48–56	74F	Chronic renal failure and related anemia	No	NA	Fatigue, difficulty with gait and articulation	Protein 69 mg/dL; glucose 78 mg/dL	High T2 signal in deep white matter of right cerebellum; small high T2 signal lesions in cerebral hemispheres	Diffuse severe demyelination in cerebellar white matter; oligodendrocytes stained positive by antibody to JC virus capsid protein (VP1) primarily in cerebrum and rarely in the cerebellum	NR	Aspiration pneumonia; death 6 months after presentation
Tatsuro Irie et al., <i>Internal medicine</i> , (1992) 31: 218–223	64F	Chronic glomerulonephritis	Yes	6	Gait ataxia	WBC 23 (80% mononuclear, 20% polymorphonuclear); protein 103 mg/dL; glucose 91 mg/dL; negative oligoclonal band IgG; elevated myelin basic protein	High signal intensity lesion in the right cerebellar peduncle and white matter of right cerebellar hemisphere	Multifocal coalescent demyelination; myelin sheaths in cerebellum and brainstem entirely replaced with reactive astrocytes; numerous oligodendroglial cells; oligodendroglial nuclei stained positive with anti JC-virus antibody	NR	Death at 4 months (sepsis)
Osamu Matsubara et al., <i>Virchows Arch [Pathol Anat]</i> (1984) 403:301–305	56M	Chronic renal insufficiency secondary to gouty kidneys	Yes	11	Behavioral change followed by speech and gait disturbance and left arm ataxia	No abnormalities	NR	Diffuse areas of demyelination in ventral pons and left cerebellar hemisphere, viral nuclear inclusions confirmed by electron microscopy	NR	Death at 5 months (respiratory failure)
B. Guillaume et al., <i>European Journal of Neurology</i> (2000) 7: 101–106	65M	Chronic renal insufficiency (etiology unknown)	No	NA	Decreased appetite, spatiotemporal disorientation and headache and apathy	Week 2–7: CSF PCR positive for JC virus	High signal intensity in right frontal white matter becoming more diffuse on subsequent MRI	Histological findings “typical of PML”	Cytarabine 2 mg/kg/day IV for 5 days (repeated 3 times every 21 days); Cytarabine 50 mg/m ² intrathecally weekly (week 2 to week 7)	Death at 7 months (cause NR)
Hiroto Matsuda et al., <i>Therapeutic Apheresis and Dialysis</i> (2006) 10(3): 291–295	57M	Chronic glomerulonephritis	Yes	10	Decreased level of consciousness, somnolence, gait, and visual disturbances	Normal cell count, protein and glucose; positive PCR for JC virus; negative oligoclonal IgG or elevated myelin basic protein	High signal intensity in the left occipital and temporal lobes	Multiple cerebral demyelination in the subcortical regions; nuclear viral particles in large oligodendroglia	NR	Death at 7 months (pneumonia)

HD: hemodialysis; NA: not applicable; NR: not reported.

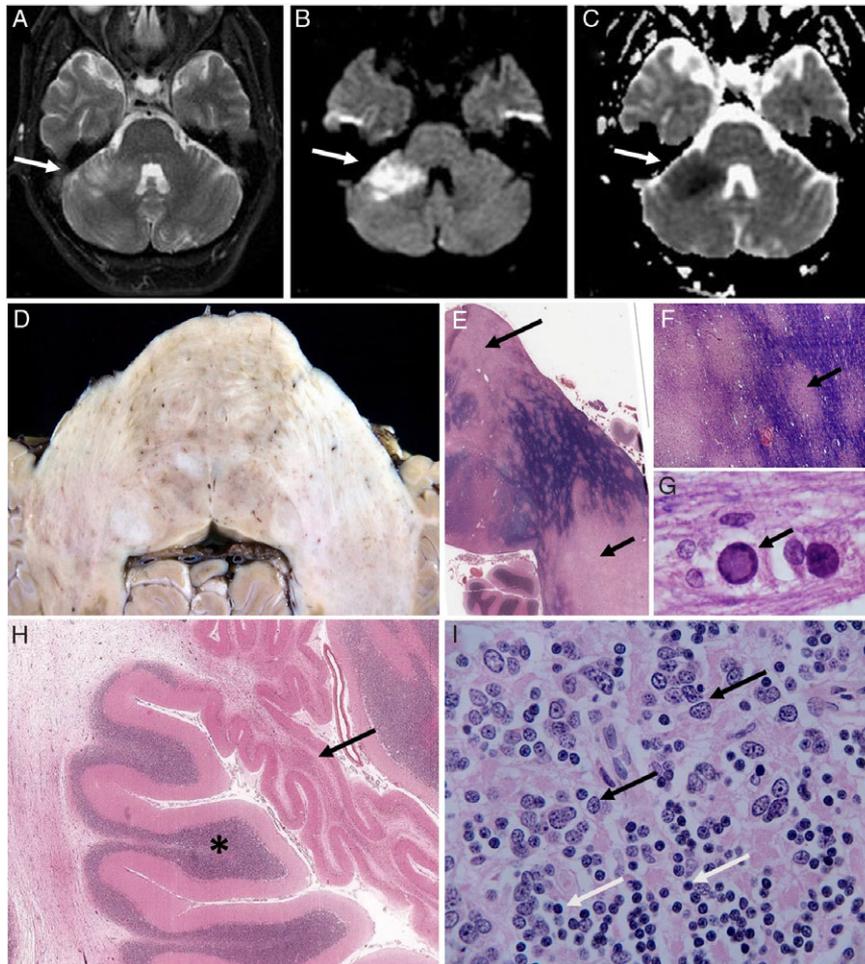


Figure 1: Axial MRI of the brain (A–C), with the right cerebellar lesion (arrows) appearing bright on diffusion-weighted imaging (DWI) sequences (A,B) and dark on apparent diffusion coefficient (ADC) sequence (C). Axial sections (D–I) showing subtle mottling of the base of the pons and middle cerebellar peduncles (D), with large pale areas of established demyelination (E, arrows) and multiple small pale foci of active demyelination (E and enlarged area F, arrow) with Solochrome Cyanine R [SCR] staining (intact myelin blue). Enlarged oligodendrocyte nuclei (arrow) containing amphophilic material (G) in area of active demyelination (SCR stain). Cerebellum (H), with atrophied area due to complete loss of internal granule cells (H, arrow; adjacent normal appearing cortex, asterisk) and a group of enlarged JCV-infected granule cells (I, representative infected cells, black arrows, compared to normal appearing cells, white arrows).

Our case highlights that although PML is a rare disease, it should be considered in patients with chronic renal failure, especially those on hemodialysis, who present with progressive unexplained neurological symptoms.

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CONFLICT OF INTEREST

The authors declare no competing interests relevant to this work.

STATEMENT OF AUTHORSHIP

All authors have seen and approved the content of the submission, and all have contributed significantly to the work. B.D. and M.B. were involved in the clinical care of the patient, prepared the written case report, and performed the initial literature review. J.R. performed neuropathological analysis of tissue, performed additional literature review, prepared histologic images, and reviewed and edited the manuscript.

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