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Anomia in a Lung Transplant Recipient

Natalie Stec
Henry Ford Health System, nstec1@hfhs.org

Stephanie B. Tancer
Henry Ford Health System, stancer1@hfhs.org

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Authors: Natalie Stec, MD, Stephanie Tancer, MD

Departments of Internal Medicine and Neurology
Henry Ford Health System; Detroit, Michigan

Background

- There have been nine documented cases world-wide of progressive multifocal leukoencephalopathy (PML) in lung transplant recipients.
- PML is a rare, sub-acute demyelinating disease of subcortical white matter caused by reactivation of the John Cunningham virus (JCV).
- PML almost exclusively occurs in immunocompromised patients, with organ transplant recipients accounting for less than 10% of cases. PML is almost invariably fatal, and survivors are often left with severe neurological impairments.

Objective

- To raise clinical suspicion of PML in lung transplant recipients presenting with neurological symptoms.

Case Description

We describe the case of a 65 year-old male who underwent bilateral lung transplantation for idiopathic pulmonary fibrosis. Initial immunosuppression included tacrolimus, mycophenolate mofetil, and prednisone.

Over the course of two years, he developed tacrolimus-induced nephrotoxicity requiring hemodialysis, leukopenia, and CMV viremia treated with intravenous gancyclovir. Several pharmacological adjustments were therefore indicated, including trials of rapamycin, sirolimus, and azathioprine. Following appropriate treatment, his initial immunosuppressives were reinstated.

Further complications included two incidents antibody-mediated rejection for which he received plasma exchange and monthly intravenous immunoglobulin (IVIg). Additionally, a single dose of rituximab (375mg/m2) was given during the second episode of rejection.

Seven months following rituximab administration, he presented to the emergency department after a syncopal episode at home. He reported several months of progressive confusion, memory loss, difficulty findings words, bilateral upper extremity tremor and generalized weakness resulting in repeated falls. His symptoms were initially attributed to tacrolimus neurotoxicity. He denied any baseline chronic neurological deficits.

Neurological examination demonstrated impaired memory, disorientation, mild dysarthria, anomic aphasia, bilateral upper extremity tremor, left lower extremity sensory deficits, and bilateral lower extremity hyperreflexia with non-sustained ankle clonus and absent Babinski responses.

Non-contrast computed tomography (CT) scans of the head and cervical spine were unremarkable. Laboratory work-up was negative for toxometabolic derangements or relevant vitamin deficiencies. Leukopenia (WBC 2.2 K/uL) prompted discontinuation of mycophenolate mofetil. He remained on prior doses of tacrolimus, prednisone, and prophylactic anti-microbial agents.

Brain MRI revealed abnormal white matter signals in the left temporooccipitoparietal junction and occipital horn of the right ventricle. No abnormalities were noted on cervical spine MRI. Initial radiological differentials included primary CNS lymphoma or nonhemorrhagic cerebral amyloid angiopathy. Lumbar puncture was significant for lymphocytic pleocytosis and positive polymerase chain reaction (PCR) for JCV DNA. CSF flow cytometry and further infectious work-up was negative.

The patient was diagnosed with PML based on clinical, radiological and CSF findings. His immunosuppressive therapy was decreased to rapamycin and prednisone. Mirtazapine was initiated for treatment of PML. Progressive decline in neurological and functional status prompted withdrawal of medical treatments and pursuit of hospice care. The patient passed away two months later.

Laboratory Data

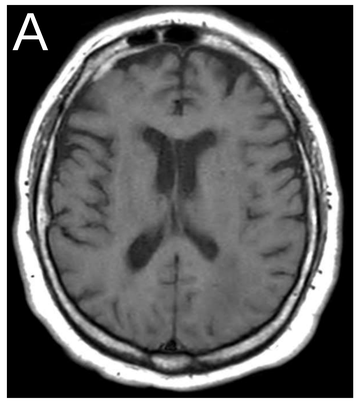
COMPLETE METABOLIC PANEL	
Sodium	136 mmol/L
Potassium	5.3 mmol/L
Chloride	102 mmol/L
Calcium	9.0 mg/dL
Carbon dioxide	31 mmol/L
Blood Urea Nitrogen	37 mmol/L
Creatinine	1.99mg/dL
Glucose	168 mg/dL
ALT	8 IU/L
AST	16 IU/L
Bilirubin, Total	0.4mg/dL
Alkaline Phosphatase	46 IU/L
Albumin	3.4 g/dL
Total Protein	5.7g/dL

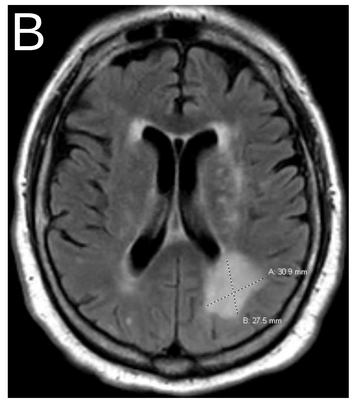
COMPLETE BLOOD COUNT	
WBC	2.2 K/uL
RBC	2.84 M/uL
Hemoglobin	8.1g/dL
Hematocrit	24%
Mean Corpuscular Volume	84.6 fl
Red Cell Distribution Width	15.8%
Platelet Count	148 K/uL
Neutrophils, Absolute	1.41 K/uL
Lymphocytes, Absolute	0.40 K/uL
Metamyelocytes, Absolute	0.13 K/uL
Atypical lymphocytes, Absolute	0.04 K/uL

VITAMINS AND MINERALS	
Copper	1012 uq/L
Zinc	61 uq/dL
Vitamin B12	329 pg/mL
Vitamin E	885 ug/dL
Vitamin D	22 ng/mL

CEREBROSPINAL FLUID	
Color	Colorless
Clarity	Clear
Glucose	78 mg/dL
Protein	47.0 mg/dL
Red Blood Cells	88 cu mm
White Blood Cells	13 cu mm
Lymphocytes	100%
Bacterial Culture with Gram Stain	Negative
Acid Fast Bacilli Culture	Negative
Fungal Culture	Negative
Toxoplasma PCR	Negative
Cryptococcal antigen	Negative
EBV DNA PCR	Negative
VZV PCR	Negative
West Nile IgG	<1.30
West Nile IgM	<0.90
Cytology	Negative
JC Virus DNA detector	Positive

Imaging





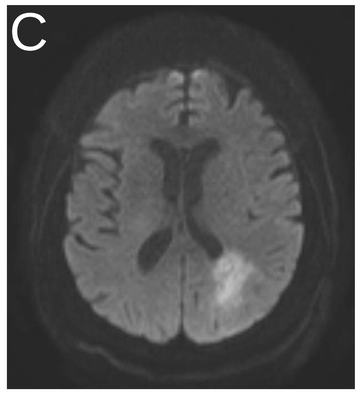


Figure 1: A: T1, B: T2 fluid attenuated inversion recovery (FLAIR), C: Diffusion-weighted imaging (DWI). Of note is an area of T2/FLAIR white matter signal abnormality corresponding to T1 hypointensity in the left temporal-occipito-parietal junction with a varying degree of restricted diffusion but no pathological enhancement. There is also a small region of confluent, T2/FLAIR signal abnormality without associated diffusion restriction adjacent to the occipital horn of the right lateral ventricle. A small focus of T2/FLAIR signal abnormality without associated diffusion restriction is seen involving the vertex of the right temporal lobe. The radiological differential included primary CNS lymphoma or non-hemorrhagic amyloid angiopathy.

Other Reported Cases

Reported Cases of PML in Lung Transplant Recipients

	Age/Sex (M/F)	Immune suppression *Anti-rejection	Mos from transplant to PML onset	Presentation	Diagnosis	Management	Outcome
Ouwens (1999)	43/M	Aza, Cyc, GC *Anti-thymocyte IgG	15	L hemianopia, seizures, R leg paresis, visual hallucinations	CSF: negative Autopsy: JCV	↓ immune suppression	Death
Shitrit (2002)	55/M	MMF, Tac, GC	7	L hemiplegia, frontal release and pseudobulbar signs, seizures	CSF: negative Biopsy: JCV -, PML Urine: BK virus	↓ immune suppression Cidofovir & probenecid	Symptom stabilizatior
Waggoner (2009)	38/F	Tac, Aza, GC *Alemtuzumab. **Anti-thymocyte IgG	48 (13*)	Ataxia, visual disturbance, dysarthria, anomia	CSF: JCV	↓ immune suppression Cidofovir, mirtazapine	Death
Mateen (2011)	39/F	Not stated	42	Ataxia	CSF: JCV	Mirtazapine, mefloquine	Death
	62/F	Not stated	27	Ataxia, L hemiparesis	CSF: JCV	Not stated	Death
Lobo (2013)	61/M	MMF, Cyc, GC *Basiliximab **Rituximab	13 (2*)	L hemiparesis, L facial centralis, memory loss, headaches	CSF: JCV	↓ immune suppression	Death
Moua (2013)	61/M	Tac, GC	5	R hemiparesis, aphasia, cognitive impairment	CSF: negative Biopsy: JCV+, PML	↓ immune suppression Cytosine arabinoside	Death
Panchabhai (2016)	60/F	Tac, GC	16	L arm weakness, R hemianopia, frontal release signs	CSF: JCV BAL: JCV	None	Death
Ishii (2019)	60/F	MMF, Tac, GC	60	Apathy, confabulation, confusion	CSF: JCV	↓ immune suppression Mefloquine	Death
Current case (2019)	65/M	MMF, Tac, Siro, Rapa, GC **Rituximab	36 (7*)	Confusion, anomia, tremor, L leg weakness and sensory deficit	CSF: JCV	↓ immune suppression Mirtazapine	Death

Legend:

Aza = azathioprine, Cyc = cyclosporine, GC = glucocorticoids, MMF = mycophenolate mofetil, L = left, R = right, Mos = months, M = male, F = female, JCV = John Cunningham virus, PML = progressive multifocal leukoencephalopathy, CSF = cerebrospinal fluid, "+" = positive, "-" = negative.

* = Immune-suppressive management of confirmed rejection

* = time in months from corresponding anti-rejection treatment and onset PML symptoms

Discussion

- Sub-acute CNS complaints with white matter changes on MRI pose a diagnostic challenge in transplant recipients. The most commonly reported differential diagnoses include infection, hematological malignancy, and toxic leukoencephalopathy (TL).
- On review of literature (see table), several reports indicated negative CSF JCV (n = 3 of 10), with diagnosis confirmed on biopsy (n = 2) or autopsy (n = 1).
- A single case of PML diagnosed on bronchoalveolar lavage (BAL) was reported by Panchaibhai et al, suggesting a possible alternate diagnostic method that may circumvent the need for biopsy.
- Shitrit et al. report the first case of PML caused by BK virus in a lung transplant recipient. The patient's symptoms improved following cidofovir and probenecid. This uncommon etiology may become clinically relevant as the prevalence of organ transplantation increases.
- JCV encephalopathy (JCVE) is a unique manifestation of JCV infection involving cerebral grey matter. Hamad, Y. et al described the first documented case of JCVE in a lung transplant recipient. In contrast to PML, the patient's clinical condition stabilized with mirtazapine.
- Several monoclonal antibodies (mAbs) are associated with the development of PML, with evidence pointing towards rituximab as a relevant contributor. Including our patient, there have been three documented lung transplant recipients (n = 3 of 10) who developed PML within 13 months of receiving rituximab.
- Available treatments for PML are limited and offer no evidence-based mortality benefit. Few accounts of clinical stabilization have been reported with early intervention, however the majority of these accounts involve non-transplant patients.
- Organ transplant recipients constitute less than 10% of total PML cases. It is postulated that PML is under-recognized and under-diagnosed in the transplant population, resulting in data that may not accurately reflect its true prevalence. Therefore, it is difficult to quantify favorable outcomes. Decreasing or discontinuing immunosuppressive therapy is generally recommended, but places the patient at increased risk of allograft rejection and death.

Conclusion

- Lung transplantation has become the standard of care for chronic end-stage respiratory failure, and the prevalence of PML may increase correspondingly.
- It is prudent to initiate urgent clinical work-up for PML in a transplant recipient presenting with neurological symptoms and white matter changes on brain imaging. Physicians should be familiar with this entity, with particular emphasis on monoclonal antibody use as a predisposing risk factor.
- When navigating a broad differential, negative initial CSF studies may result in delayed diagnosis and management. Although treatment options are of dubious benefit, some accounts of favorable outcomes have been reported with early modulation of immunosuppression. Maintaining high clinical suspicion of PML and earlier pursuit of definitive testing such as brain biopsy may be life-saving.

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