Published in final edited form as:

J Neurovirol. 2011 October ; 17(5): 500–503. doi:10.1007/s13365-011-0045-2.

Progressive Multifocal Leukoencephalopathy Associated with Isolated CD8+ T-Lymphocyte Deficiency Mimicking Tumefactive MS

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Abstract

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system (CNS) caused by lytic infection of oligodendrocytes by the polyomavirus JC (JCV). PML has classically been described in individuals with profound cellular immunosuppression. While some case reports have documented PML in individuals with minimal or occult immunosuppression, such cases are very rare and their pathogenesis is not well understood. We report a unique case of a 74 year-old woman who developed PML clinically mimicking tumefactive multiple sclerosis in the context of an idiopathic isolated CD8+ T-lymphocytopenia. Her course subsequently stabilized, concomitant to the development of a cellular immune response directed against JCV. We review the current literature of related cases and discuss the pathogenesis and implications of this rare presentation.

Keywords

progressive multifocal leukoencephalopathy; JC virus; immunodeficiency; demyelination

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a devastating demyelinating disease of the central nervous system (CNS) caused by the DNA polyomavirus JC (JCV). While

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DECLARATION OF INTEREST: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

This report has not been published or presented elsewhere. No honorarium, grant, or other form of payment was given to anyone to produce the manuscript.

latent JCV infection is reportedly present in up to 80% of healthy adults (Boothpur & Brennan, 2010), PML is rare, with an incidence of about 0.6 cases per million (Weber, 2008). Profound cellular immune suppression appears to play a role in reactivation of JCV and development of PML (Tan & Koralnik, 2010). Following even transient cellular immunosuppression, infected B-lymphocytes may carry a genetically altered JCV to the CNS (Boothpur & Brennan, 2010; Koralnik, 2006; Sabath & Major, 2002), where this neurovirulent JCV progressively lyses oligodendrocytes and astrocytes.

Most HIV-infected PML patients have a profound CD4+ T-lymphocytopenia, but PML may also occur in patients with minimal or occult immunosuppression (Gheuens, Pierone et al., 2010). A key determinant of PML activation and severity of disease resides in the host's ability to mount a vigorous cellular immune response against JCV (Du Pasquier, Autissier et al., 2005). CD4+ T-lymphocytes are important in host defense against JCV because they stimulate a cytotoxic response mediated by CD8+ T-lymphocytes (Koralnik, 2004). JCV-specific CD8+ cytotoxic T-lymphocytes (CTL) actively destroy JCV-infected glial cells, thereby containing PML (Du Pasquier, Autissier et al., 2005; Koralnik, 2006).

PML has not been previously reported in the setting of isolated deficiency of CD8+ T-lymphocytes. We report the case of a woman with idiopathic CD8+ T-lymphocyte deficiency who developed PML, presenting initially like tumefactive multiple sclerosis.

CASE REPORT

A 74 year-old woman without history of known immunodeficiency developed acute dysarthria and left hemiplegia one month following pelvic surgery for removal of a benign ovarian serous cystadenoma. MRI of the brain revealed two ring enhancing lesions (the largest of which was in the right frontal lobe and showed central necrosis) and scattered white matter abnormalities. (Figure 1 A–D). MR spectroscopy was consistent with lymphoma or demyelination (data not shown). Brain biopsy revealed extensive inflammatory infiltrates composed of T- and B-lymphocytes, plasma cells and macrophages with relative preservation of axons, consistent with acute fulminant demyelination (Figure 2). Blood work, including erythrocyte sedimentation rate, C-reactive protein, serum protein electrophoresis, antinuclear antibody, anti-Ro antibody, anti-La antibody, rapid plasma regain, antineutrophil cytoplasmic antibodies, myeloperoxidase antibodies, Lyme serologies, and HIV ELISA, was normal. There was no evidence of neoplasm. Cerebrospinal fluid (CSF) analysis demonstrated normal cells and protein, positive oligoclonal bands, an elevated immunoglobulin G index of 1.81 (normal: 0.28–0.66), and an elevated myelin basic protein of 20.50 mg/dL (normal: 0–1.10). Based on the CSF analysis, imaging, and preliminary biopsy results, the patient was treated for an atypical case of presumed tumefactive multiple sclerosis (MS) with methylprednisolone 1000mg IV daily for 6 days followed by an oral steroid taper.

CSF JCV polymerase chain reaction (PCR) subsequently returned positive. Two repeat lumbar punctures were performed 11 and 13 days later, each showing normal cells and protein. JCV PCR on the second sample was indeterminate, and on the third was negative. Biopsy pathology later demonstrated JCV infection of glial cells by fluorescent in situ hybridization (FISH), confirming PML. Double immunohistochemistry staining showed inflammatory T cell infiltrates, harboring equivalent numbers of CD8+ and CD4+ T cells (Figure 2). The patient had a detectable cellular immune response against JCV in her blood, measured by serial enzyme-linked immunosorbent spot (ELISpot) and intracellular cytokine staining (ICS) (Table 1). Serial analysis of T lymphocyte subsets demonstrated a persistently reduced CD8+ T-lymphocyte count in the context of a normal absolute CD4+ T-lymphocyte count (Table 2).

The patient was treated with mirtazapine 15mg nightly (Cettomai & McArthur, 2009) for 5 months (discontinued due to paranoid and tangential thoughts) and mefloquine (Brickelmaier, Lugovskoy et al., 2009) 250mg daily for 3 days, then 250mg weekly for 9 months. She regained partial strength in her left leg 17 weeks after admission. Follow-up MRI 10 months after the initial study revealed no new demyelinating lesions and decreased enhancement throughout (Figure 1 E–H). She has since remained clinically stable with moderate paranoia and irritability, full paresis of the left upper extremity, and partial strength of the left lower extremity 11 months after her initial presentation.

DISCUSSION

Isolated CD8⁺ T-lymphocyte deficiencies are rare and their clinical implications are poorly understood (Gergely, 1999). They occur most often in the context of a CD4⁺ T-lymphocyte deficiency, such as in combined variable immunodeficiency (CVID) (Gergely, 1999). Several PML cases have been described in CVID, only one of which also demonstrated a marked deficiency in peripheral memory CD8⁺ T-lymphocytes (Narula, Larosa et al., 2007). While PML has not previously been linked to an isolated CD8⁺ T-lymphocytopenia, one could easily propose a mechanism of pathogenesis given the role of cytotoxic T-lymphocytes in containing JCV infection. It is noteworthy that our patient stabilized despite persistently low CD8⁺ T-lymphocyte counts. She was, however, able to mount an adequate anti-JCV cellular response, mediated by both CD8⁺ and CD4⁺ T cells (Table 1). We have recently demonstrated the role of these two T lymphocyte subtypes in the containment of PML (Gheuens & Bord, 2011). This immune reaction may have caused the enhancement seen on the patient's initial MRI (Epker, Biezen et al., 2009), which is seen in up to 15% of individuals with PML (Berger, Pall et al., 1998), and has been correlated with better prognosis (Berger, Levy et al., 1998; Korallnik, 2006). This case is demonstrative of the changing face of PML as we see more cases over time in HIV patients, patients on immunomodulatory therapy, and those with either minimal or occult immunosuppression (Vermersch, Kappos et al., 2011).

Why our patient with a presumably chronic CD8⁺ T-lymphocytopenia developed PML at this time remains unclear. She had recently undergone surgery, which may have led to a further global transient immune suppression (Hogan, Peter et al., 2011). Some suggest that transient immune suppression instigates changes in the JCV genome regulatory region, leading to sequences of varying biologic activity (Sabath & Major, 2002), and perhaps the emergence of more neurovirulent JCV. It is possible that the patient became viremic with more aggressive JCV strains, and that her CD8⁺ T-lymphocytopenia failed to prevent JCV translocation into the CNS and the development of PML. Of note, ovarian serous cystadenomas have not been specifically associated with immunologic aberrations.

We would also like to mention that while we did ultimately treat this patient with mirtazapine and mefloquine, these are not definitively proven treatments of PML. A multi-center treatment trial with mefloquine was recently terminated after interim analysis found that this medication failed to reduce JC viral DNA levels in the cerebrospinal fluid (Friedman, 2011). Given our patient's only partially suppressed immune status, she may have recovered without treatment. However, given the unclear pathogenesis of the appearance of her lesions, we decided to be as aggressive as possible with therapeutic agents that have a minimal risk profile.

Interestingly, the initial clinical diagnosis was tumefactive MS. Whether JCV may be a trigger for MS in a small subset of patients has been a matter of debate (Boerman, Bax et al., 1993; Ferrante, Omodeo-Zorini et al., 1998; Stoner, 1991). This case invites us to revisit the clinical and pathological spectrum of demyelinating diseases, and particularly the role of

JCV in tumefactive MS lesions. When considering a differential diagnosis, many of these lesions may appear similar on MRI, and there may be some pathological overlap as well. It is possible that JCV acts as a trigger in tumefactive MS (Nishimura, Kamikura et al., 1993), or that cases previously diagnosed as tumefactive MS may in fact be PML in minimally immunosuppressed individuals who are then able to mount a sufficient immune response to control progression of the lesions. Given these considerations, clinicians may want to measure T-cell subsets in blood and look for JCV DNA in CSF of patients presenting with atypical demyelinating lesions, or lesions consistent with tumefactive MS.

Acknowledgments

Dr. McGuire received support from NIH grant T32-NS061779 and from the L. Morton Morley Funds of The Philadelphia Foundation. Dr. Koralnik has received honoraria from Bristol-Myers Squibb, Ono Pharmaceuticals, Merck Serono, Antisense, and Alnylam, and is supported in part by NIH grants R01 NS 041198 and 047029 and K24 NS 060950 and a research grant from Biogen Idec. Dr. Jacobs has received honoraria from Biogen Idec, Teva Pharmaceuticals, and Serono. The content is the sole responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Figure 1.

MRI brain. Initial Presentation (top row): axial FLAIR showing tumefactive lesion in the right frontal lobe white matter extending to the subcortical white matter of the temporal lobe (A and B), axial T1 + gadolinium showing ring enhancement of the lesions (C and D). 10-month follow-up (bottom row): axial FLAIR showed residual lesions in the right frontal and temporal lobe white matter and left periventricular area, associated with atrophy (E and F), axial T1+ gadolinium demonstrating absence of enhancement in the lesions (G and H).

Figure 2.

Right frontal lobe pathology. A: Hematoxylin and eosin stain of biopsied lesion showing extensive inflammatory infiltrate. B: JCV in situ hybridization demonstrating JCV+ cells. C: Double Immunohistostaining showing equal numbers of CD8+ (brown) and CD4+ T cells (blue, CD3+/CD8-). Antibodies: Vector VP-C325 CD8 (1A5) & Novocastra NCL-L-CD3-PS1.

Table 1Serial Immunologic Assays^a for JCV

Weeks since symptom onset	ELISpot	ICS CD4	ICS CD8
13	+	-	+
35	+	+	+
54	+	+	+

Table 2

Serial WBC, ALC, CD4+ lymphocyte, and CD8+ lymphocyte counts

	Weeks since symptom onset					Reference Range
	0	10	12	25	51	
WBC (x10 ³ /μL)	7.5	14.6	7.1	7.3	6.6	4.0–11.0
ALC (x10 ³ /μL)	1.1	1.5	1.5	1.09	1.5	1.0–5.0
CD4+ (absolute count/μL)	-	1150	1117	715	1137	560–1840
CD4+ (%)	-	76	76	66	75.8	32–56
CD8+ (absolute count/μL)	-	60	76	61	75	260–1230
CD8+ (%)	-	4	5	6	5.0	15–40
CD4+/CD8+ ratio	-	19.2	15.2	11.0	15.16	0.9–3.4

WBC: white blood cell, ALC: absolute leukocyte count, reference range taken from the University of Pennsylvania Department of Pathology and Laboratory Medicine