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Review

T cell deficiencies as a common risk factor for drug associated progressive multifocal leukoencephalopathy

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ABSTRACT

Progressive multifocal leukoencephalopathy (PML) is a disease of the central nervous system caused by neuropathogenic prototypes of ubiquitous community-acquired JC virus (JCV). The disease became of particular concern following its association with certain therapies that modulate immune system function without heavy immunosuppression. Due to lack of prophylactic/treatment options and poor outcomes, which often include severe disability or death, PML is a considerable concern for development of new drugs that interfere with immune system functions. In this review of clinical and research findings, we discuss the evidence that deficiencies in $CD4^+$ T helper cells, cytotoxic $CD8^+$ T cells, and interferon gamma are of crucial importance for development of PML under a variety of circumstances, including those associated with use of various drugs, regardless of differences in their mechanisms of action. These deficiencies apparently enable transformation of the harmless JCV archetype into neuropathogenic prototypes, but the site(s), and the mechanisms, of this transformation are yet to be elucidated. Here we discuss the evidence for brain as one of the sites of this transformation, and propose a model of PML pathogenesis that emphasizes the central role of T cell deficiencies in the two life cycles of the JCV, one non-pathogenic and one neuropathogenic. Finally, we conclude that the development of clinical grade T cell functional tests and more consistent use of already available laboratory tests for T cell subset analysis would greatly aid the effort to more accurately predict and assess the magnitude of PML risk for concerned therapeutic interventions.

1. Introduction

Progressive multifocal leukoencephalopathy (PML) is a demyelinating infectious disease of the brain caused by neuropathogenic prototypes of ubiquitous community-acquired JCV. The disease affects relatively few individuals, even in high-risk populations such as heavily immunosuppressed patients. What distinguishes PML as a special concern is lack of prophylactic and treatment options; poor outcomes, which often include severe disability or death; and, of particular importance, it's rare but seemingly strong association with certain therapies that modulate immune system function.

During the human immunodeficiency virus (HIV) pandemic, before the implementation of highly effective antiretroviral therapy (HAART), PML was primarily observed as one of the clinical manifestations of acquired immunodeficiency syndrome (AIDS) (Berger et al., 1998). Within this population, PML has been strongly associated with a severe deficit of $CD4^+$ T cells (Engsig et al., 2009). PML has also been rarely observed in heavily immunosuppressed patients with a history of hematological malignancy (Molloy and Calabrese, 2009), transplantation (Mateen et al., 2011), congenital immunodeficiency (Hatchwell, 2015), or autoimmune disease (Molloy and Calabrese, 2009). Following the advent of HAART and subsequent decline in the incidence of AIDS, interest in PML lessened. However, interest was renewed after association of PML with natalizumab, a therapeutic monoclonal antibody approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) and Crohn's disease.

The unexpected, but highly significant association between natalizumab and PML had a considerable impact on other immunomodulating therapies. Natalizumab was the first drug to receive a label warning for PML (Tysabri, 2006), but as of today, at least 14 drugs approved by the Food and Drug Administration, 9 monoclonal antibodies (Raptiva, 2009; Entyvio, 2014; Adcetris, 2016; Gazyva, 2016; Arzerra, 2016; Tysabri, 2016; Rituxan, 2016; Nulojix, 2017; Benlysta, 2017) and 5 small molecules (Prograf, 2015; Gilenya, 2016; Jakafi,

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Table 1
Medications with PML label warnings.

Drug	Indication	Target Molecule	Target Cell Type	Mechanism of Action
Biological drugs				
Belatacept	Kidney transplantation	CD80, CD86	APCs, activated T cells	T cell costimulation blocker
Belimumab	SLE	BLyS	B cells	Decreased B-cell survival
Brentuximab vedotin	Hodgkin lymphoma	CD30	Type 2 T-helper cells	Kills type 2 T-helper cells and inhibits T-helper–mediated B-cell activation
Efalizumab	Psoriasis	CD11a (LFA-1)	Leukocytes	Inhibits leukocyte activation and transmigration
Obinutuzumab	B-CLL	CD20	B cells	Kills $CD20^+$ B lymphocytes
Ofatumumab	B-CLL	CD20	B cells	Kills $CD20^+$ B lymphocytes
Natalizumab	RRMS Crohn's disease	$\alpha_4\beta_1$- and $\alpha_4\beta_7$-integrin	Leukocytes	Prevents leukocyte transmigration through blood-brain barrier
Rituximab	B-CLL Non-Hodgkin lymphoma Rheumatoid arthritis Wegener granulomatosis Microscopic polyangiitis	CD20	B cells	Kills $CD20^+$ B lymphocytes
Vedolizumab	Ulcerative colitis Crohn's disease	$\alpha_4\beta_7$-integrin	T cells	Prevents homing of memory T cells into the gut
Small molecule drugs				
Dimethyl fumarate	RRMS	Nuclear factor F2 (Nrf2)	Lymphocytes	Immunomodulator, cytoprotector
Fingolimod	RRMS	Sphingosine-1 phosphate receptor (S_1PR)	Lymphocytes	Immunomodulator, cytoprotector
Ruxolitinib	Myelofibrosis	JAK1, JAK2	Broad; all blood cells	Inhibits interferon gamma–mediated signaling
Sirolimus	Transplantation	FKBP12	T and B cells	Prevents T- and B-cell activation
Tacrolimus	Transplantation	Calcineurin, PG-E2, P glycoprotein	T cells	Prevents T cell activation

APC = antigen-presenting cell; B-CLL = B-cell chronic lymphocytic leukemia; BlyS = B-lymphocyte stimulator; FKBP12 = 12-kDa FK506 binding protein; IMPDH = inosine-5′-monophosphate dehydrogenase; JAK = Janus kinase; JNK = c-Jun N-terminal kinase; PG-E2 = prostaglandin E2; RRMS = relapsing-remitting multiple sclerosis; SLE = systemic lupus erythematosus.

2016; Rapamune, 2016; Tecfidera, 2017), have had PML warnings included in their prescribing information (Table 1). For most of these drugs, the evidence for an association with PML is much less convincing than for natalizumab. In the case of one drug, vedolizumab, the PML warning is based entirely on the undifferentiated risk for integrin inhibitors class of drugs, such as natalizumab, and in the absence of an actual observed PML case (Entyvio, 2014). Unlike natalizumab, vedolizumab does not prevent leukocyte transmigration through the blood-brain barrier (BBB) (Haanstra et al., 2013), and during clinical trials and nearly 3 years of postmarketing experience, there were no reports of vedolizumab-associated PML (AERS and Vigibase databases searches as of 12 April 2017). With regard to other drugs, the warning is mostly based on a relatively small number of cases observed in populations such as patients with blood cancer and autoimmune disease. However, these patient populations probably have an increased risk for PML, due to the nature of their diseases and use of concomitant immunosuppressive therapies, thus the actual risk is difficult to assess.

The first link between PML and a specific immune system deficit, a decline in $CD4^+$ T cell count, was established during the AIDS/HIV pandemic of the 1980s (Berger et al., 1998). A long term follow-up registry of individuals with HIV infection demonstrated that $CD4^+$ T cell deficit is a significant risk for PML, particularly with a $CD4^+$ T cell nadir of < 200 cells/μL (Engsig et al., 2009). In addition to $CD4^+$ T cells, $CD8^+$ T cells are of crucial importance for survival and recovery from PML in this patient population. JCV-specific $CD8^+$ T cells were found to be present only in survivors of HIV infection associated PML, but not in those with progressive disease (Du Pasquier et al., 2003; Koralnik et al., 2002). Because low $CD4^+$ T cell count is a hallmark of HIV/AIDS, differential diagnosis of suspected PML typically includes testing for HIV and $CD4^+$ T cell counts. This practice led to the discovery that $CD4^+$ T cell is an important factor in pathogenesis of PML beyond individuals with HIV infection (Haider et al., 2000).

$CD4^+$ and $CD8^+$ T cell deficiencies are also described in literature reports of individual PML cases in association with variety of conditions. After conducting an extensive review of the literature for reports of PML not associated with HIV infection, we identified 84 individual PML cases that describe peripheral blood lymphocytes, many with detailed data on $CD4^+$ and $CD8^+$ T cells (Table 2) (Alstadhaug et al., 2014; Bagnato et al., 2001; Balduzzi et al., 2011; Bartsch et al., 2015; Berciano et al., 2003; Berger et al., 2014; Berghoff et al., 2013; Bonavita et al., 2008; Chabwine et al., 2012; Chiarchiaro et al., 2010; Christakis et al., 2013; Cid et al., 2000; Day-Williams et al., 2015; De Raedt et al., 2008; Delgado-Alvarado et al., 2013; D'Souza et al., 2010; Fianchi et al., 2010; Fleischmann, 2009; Focosi et al., 2007; Gheuens et al., 2010; Gofton et al., 2011; Goldberg et al., 2002; Gonzalez et al., 1999; Govindappa et al., 2007; Granot et al., 2009; Grewal et al., 2016; Gupta et al., 2016; Gupta et al., 2012; Haider et al., 2000; Heine et al., 2013; Hequet et al., 2002; Herold et al., 2012; Hohlfeld et al., 2012; Inhoff et al., 2007; Iwase et al., 1998; Keith et al., 2012; Kesari et al., 2008; Kharfan-Dabaja et al., 2007; Kishida and Tanaka, 2010; Kranick et al., 2007; Kunschner and Scott, 2005; Kurmann et al., 2011; Le Roux-Villet et al., 2010; Lefevre et al., 2009; Lehmann et al., 2015; McGuire et al., 2011; Meister et al., 2014; Miskin et al., 2016; Murayi et al., 2015; Nanda, 2016; Neeb et al., 2009; Osorio et al., 2002; Owczarczyk et al., 2007; Patel et al., 2010; Pelosini et al., 2008; Przepiorka et al., 1997; Puri et al., 2010; Reilmann et al., 2005; Rey et al., 2007; Rueger et al., 2006; Saad et al., 2000; Sano et al., 2015; Saumoy et al., 2002; Shprecher et al., 2008; Takeda et al., 2009; Tan et al., 2011a; Vaklavas et al., 2010; van der Kolk et al., 2016; Vandecasteele et al., 2005; Verma et al., 2007; Viallard et al., 2007; Visco et al., 2009; Warnatz et al., 2003; Wathes et al., 2013; White et al., 2002; Yagi et al., 2012; Yokoyama et al., 2008; Yoshida et al., 2014; Yoshida et al., 2015; Zhang et al., 2010). The majority of reviewed PML cases that report T cell levels, either descriptively (low, normal, or high) or with detailed cell counts, show both $CD4^+$ and $CD8^+$ T cell deficiency. In 68% of the cases reviewed, $CD4^+$ T cell count was low, and in 55%, $CD4^+$ T cell count was < 200 cells/μL. $CD8^+$ T cell count was low in 58% of the cases reviewed. Three major confounding conditions for these reports were hematological malignancy, autoimmune disease, and idiopathic lymphocytopenia, all showing similar trends in association of PML with low $CD4^+$ and $CD8^+$ T cell counts.

In this review we discuss the evidence for deficiency of $CD4^+$ and $CD8^+$ T cells in PML associated with natalizumab and rituximab, biological drugs with boxed warning for PML, and dimethyl fumarate, a small molecule drug with recently identified PML risk. These drugs have been chosen as typical representatives of the three classes of drugs