Progressive Multifocal Leukoencephalopathy in Patients on Immunomodulatory Therapies*

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Key Words

demyelination, viral latency and reactivation, cell tropism factors, immune system dysfunction, biological therapies for autoimmune diseases

Abstract

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the white matter of the human brain caused by lytic infection of oligodendrocytes with the human polyomavirus JCV. Although the majority of PML cases occur in severely immune-suppressed individuals, with HIV-1 infection as the predominant factor, PML has been increasingly diagnosed in patients treated with biological therapies such as monoclonal antibodies that modulate immune system functions. Monoclonal antibodies that target the cell adhesion molecules VLA-4 (natalizumab; Tysabri® for multiple sclerosis and Crohn's disease) or LFA-1 (efalizumab; Raptiva® for severe forms of plaque psoriasis) to prevent extravasation of inflammatory T cells into tissues, or target the cell surface marker CD20 (rituximab; Rituxan® for hematologic malignancies and rheumatoid arthritis) to deplete peripheral circulating B cells, have all been associated with PML. The link between the effects of these therapies on the immune system and the occurrence of PML has prompted investigations on JCV sites of latency in the bone marrow, the migration of bone marrow derived cells into the circulation, and intracellular virus entry into the brain.

INTRODUCTION

The neuropathological description of progressive multifocal leukoencephalopathy (PML) was reported in 1958 following examination of brain tissue in two cases of chronic lymphocytic leukemia and one case of Hodgkin's lymphoma (1). Although there were prior reports of similar pathology (2), the details of the neuropathology were aligned with underlying clinical conditions, giving rise to the name PML. Its cause was not known until viral particles were observed using electron microscopy in PML brain lesions in 1965 (3) and then isolated in cultures of human fetal brain in 1971 (4). The designation of JC virus (JCV) came from the initials of the patient whose brain tissue was used for culture and isolation. For several decades, PML was considered a very rare, virus-induced demyelinating disease of the white matter occurring in immune-compromised patients, although sero-epidemiological studies indicate exposure to JCV is globally widespread in the population. The incidence of PML rose sharply in the mid-1980s with the pandemic of HIV-1 infection and continues as an AIDS-defining illness at a rate of ~3% of HIV-1 seropositive individuals.

Recently, PML has been described in another, more unexpected population: in patients with autoimmune diseases treated with biological therapies that do not directly suppress immunity but rather dramatically alter normal immune functions. Two of these biologicals are monoclonal antibodies (natalizumab and efalizumab) that bind α-integrin molecules on the surface of T and B cells, preventing their entry into brain, gut, and skin. Another is a monoclonal antibody (rituximab) that binds the CD20 surface molecule on B cells, causing their depletion from the peripheral circulation through complement-mediated cytolysis. There is a strong link between JCV infection in cells of the immune system and in cells of the nervous system, which points to the importance of the tissue origin of JCV latency. The emergence of PML in patients treated with natalizumab, rituximab, efalizumab, and other immune-altering drugs spotlights that observation and provides new insights into the pathogenic mechanisms of JCV infection leading to CNS disease.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY IS A VIRUS-INDUCED DEMYELINATING DISEASE OF THE HUMAN BRAIN

The pathological lesions of PML are typically demyelinated plaque areas with irregular borders, surrounded by macrophages and bizarre-appearing astrocytes with large, multiple nuclei. The nuclei of infected oligodendrocytes are substantially enlarged owing to assembly of mature virion particles that tend to remain intranuclear, as seen in **Figure 1**. Infectious virus is disseminated to neighboring oligodendrocytes gradually as cell death occurs through a necrotic, lytic process (5), although apoptosis leading to cell degeneration may also occur (6). Because of this process, lesions progressively enlarge over time (weeks to months) and may become confluent. Consequently, plaque lesions are usually asymmetrical and diffuse with ill-defined borders. They are seen in subcortical white matter in the cerebral hemispheres and in some cases in the cerebellum. On MRI, the lesions can be hyperintense on T2-weighted and FLAIR (fluid-attenuated inversion recovery) sequences and hypointense on T1-weighted sequences. The lesions can be located adjacent to the cerebral cortex with damage to the U fibers (**Figure 1**). PML lesions usually do not show edema, mass effect, or gadolinium enhancement, characteristics that help differentiate these lesions from those of multiple sclerosis (7).

A classic triad of clinical signs initiates a diagnosis of PML. Cognitive impairments are typical of a subcortical dementia, with mental slowness, disorientation, and behavioral changes, and may be the first indication of PML (8). Motor dysfunctions, demonstrated by lack of coordination, gait disturbances, ataxia, and hemiparesis, are frequent and can be as

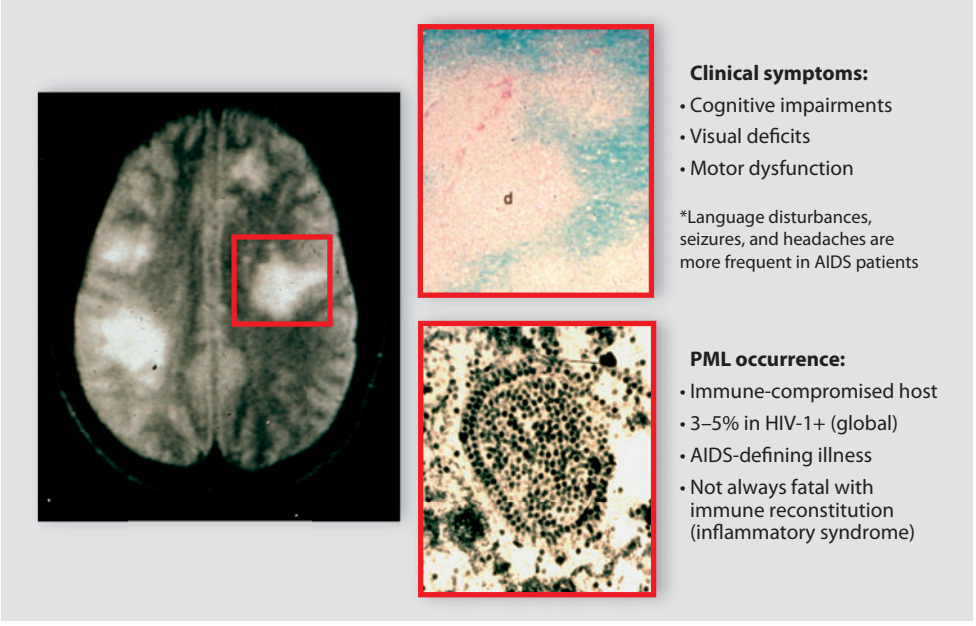

Figure 1

Progressive multifocal leukoencephalopathy (PML). *Left:* MRI scan of bilateral multifocal, subcortical demyelinated lesions in the cerebral hemispheres of a PML patient. A representative lesion outlined in red is shown on histopathology (*top center*) with a demyelinated plaque (d) on luxol fast blue stain resulting from lytic infection with the human polyomavirus JCV. *Bottom center:* Mature virion particles are shown assembled in a crystalline array in the nucleus of an oligodendrocyte. *Right:* The predominant clinical aspects and occurrence of PML are highlighted.

common as cognitive problems at the time of suspicion of PML. Visual deficits such as hemianopsia can be present. Other clinical signs that are not as common are seizures, language problems, and headaches. The clinical course of PML has been described as progressive and nearly always fatal; death occurs from weeks to months after the time of diagnosis. However, more recently with highly active antiretroviral therapy (HAART) for AIDS patients, which dramatically reduces HIV-1 in the blood and restores immune system functions, as many as 10%–20% of PML patients are surviving much longer with some resolution of PML lesions. This "immune reconstitution," with elevation of CD4 and CD8 T cells, can result in inflammation or IRIS (immune reconstitution inflammatory syndrome) in the brain (9, 10, 11). PML patients who demonstrate IRIS undergo steroid therapy to dampen their T cell responses with the hope that JCV-infected cells can still be cleared from the brain. Patients with substantial levels of CD8+ cytotoxic T cells specific to the viral capsid protein have a better prognosis that correlates with a less progressive course of disease (12, 13). No such correlation exists with humoral immunity; PML patients have substantial antibody titers to the same viral capsid protein before and during disease (14). The majority of the population has antibodies to JCV that remain throughout life. However, the neutralizing/protective role of antiviral antibody is not understood (15).

Patients with clinical progression and MRI evidence of characteristic lesions can be diagnosed with PML. However, other encephalopathies such as HIV-1-associated brain infection or CNS tumors can complicate the diagnosis. Evidence of the presence of JCV DNA or protein is considered the defining

criterion for a confirmation of PML. Immunocytochemistry using antibodies that detect viral proteins in brain tissue has been employed, but because these antibodies are cross reactive to other viruses, their specificity is not reliable. In situ DNA hybridization using probes that are highly specific to JCV DNA can be readily used in biopsy and autopsy tissues (16). However, this method requires biopsy samples that are not always available. Recently, quantitative polymerase chain reaction (qPCR) (17) detection of JCV DNA has been shown to detect down to 10 copies per milliliter of viral DNA in tissues, including cerebrospinal fluid (CSF), the most widely used clinical sample for the confirmatory diagnosis of PML. Therefore, CSF testing using qPCR has become the current diagnostic standard, showing 98% specificity and >90% sensitivity depending on the laboratory. In order to normalize the qPCR test to insure uniform reliability in commercial, hospital, or academic laboratories, a consortium of highly experienced investigators is preparing protocols and international standards following a study of blind testing of proficiency samples organized and evaluated by Quality Control for Molecular Diagnostics, an independent organization in Glasgow, Scotland.

The large literature on the biology and molecular characteristics of JCV is summarized in a recent chapter on the Polyomavirus family (18). JCV may be unique among neurovirulent viral infections in the human brain for several reasons. Although the α 2–6–linked sialic acid viral receptor, and its coreceptor 5HT2A, is found on many cell types (19), JCV demonstrates a very narrow cellular host range. JCV productively infects oligodendrocytes and astrocytes of the human brain, stromal cells in tonsillar tissues, and at low levels some CD20+ B cells and CD34+ hematopoietic stem cells. JCV infection has not been found in cerebral neurons nor in human neuronal cultures, but there are reports of infection in cerebellar granule neurons in patients with motor dysfunctions and not typical PML (20, 21). This observation suggests the possibility that other CNS diseases besides PML are associated with JCV infection (22). The host range for JCV may be controlled at the intracellular level, in the nuclei, dependent on host cell transcription factors that recognize the viral promoter DNA sequences for viral RNA and protein synthesis. Because viral DNA is infectious, the cellular receptor can be bypassed in the laboratory by directly placing JCV DNA into cells. Even following viral DNA transfection into a wide range of cell types in culture experiments, infection takes place only in those cells in which evidence for infection comes from clinical tissues. Such cells share common DNA binding proteins that promote infection (23). This observation has directed the studies of viral pathogenesis. Viral-cellular events are traced from initial sites of infection that give rise to antibody production, to sites of viral latency and reactivation, to the spread of virus to the brain, followed by glial cell infection and demyelination. Cell models in laboratory culture experiments that reflect the clinical course of JCV infection in PML patients have thereby laid the framework for studies of PML pathogenesis.

PATHOGENESIS OF PML FROM VIRAL LATENCY TO DEMYELINATION

PML remains a relatively rare disease. Its highest incidence is in AIDS patients, ~3% of HIV-1-infected individuals. This level has been consistent in many countries and has remained stable even with HAART. In addition to severe immune suppression, there appear to be synergistic interactions between HIV-1 and JCV that contribute to the higher incidence of PML in AIDS patients (24, 25). In patients with underlying neoplastic diseases or those undergoing immune suppression as allograft recipients, PML occurs much less frequently. Because of the widespread nature of JCV infection and the association of PML with immune suppression, it is generally thought that viral reactivation from sites of latency triggers the initiating event that leads to infection and destruction of the oligodendrocyte. The number of individuals who have latent infections

following exposure to JCV is not known. Three organ systems are currently thought to harbor latent infection: the kidney/urinary system, the brain, and bone marrow/lymphoid tissues.

Several studies have shown that 10%–30% of the global population shed JCV in the urine, indicating kidney latency, mostly with no pathological significance (18). Interestingly, the arrangement of the viral regulatory sequences found in urine-derived virus is substantially different from that found in virus found in pathologically affected tissues such as brain and lymphoid tissue. Data from some studies suggest that the kidney-derived regulatory sequences may undergo rearrangement during (extensive) DNA replication that would ultimately resemble those found in pathological tissues. But the virus that is isolated from urine is not infectious for human glial cells and poorly infectious for epithelial cells in culture. This is puzzling, since large amounts of virus can be shed in the urine that cannot be readily grown in kidney cells in culture. Alterations of the viral genome sequence might also take place in the capsid protein, in addition to the regulatory region, that binds specific cell receptors. For example, there is a recent report of the possibility of a more neurovirulent phenotype of JCV based on analysis of gene sequences of its capsid protein used for cell attachment identified from PML brain tissue compared with capsid protein sequences in kidney isolates from non-PML individuals (26).

Several studies examining non-PML, normal brain tissue have suggested that virus might enter or persist in the brain as a latent infection that might not be cleared under circumstances of immune suppression, leading to a productive infection in oligodendrocytes and PML (27, 28). Although this may occur, it does not seem likely that long-term latency could be established in the brain without inflammatory consequences during viral clearance. Considering the rarity of PML, the probability that the brain harbors JCV DNA as a functional site of latency may be small, but it certainly warrants further examination using many more brain samples in a controlled study.

Because of the close association of PML with the immune system, lymphoid tissues from PML patients have been examined for evidence of JCV infection. In situ DNA hybridization of AIDS patients' tissues revealed JCV DNA sequences in spleen and bone marrow (29), as well as in peripheral B cells (30). Tonsil tissue, as well as lymphocytes from tonsils taken from juvenile non-PML patients, also had JCV DNA (31), and stromal cells from tonsillar tissue were shown to be highly susceptible to JCV infection in culture, as were CD34+ cells and B lymphocytes in culture (32). In non-AIDS PML patients, bone marrow biopsy tissues that were taken months to years prior to the development of PML (**Figure 2**) also showed JCV DNA sequences that were similar if not identical to those sequences from the patients' brain tissues at the time of diagnosis of PML (8, 33). A recent study of bone marrow from HIV-positive and -negative patients with or without PML showed a high prevalence of bone marrow tissues with JCV DNA as well as expression of the viral T protein (34). JCV DNA can also be found in plasma or serum from PML and non-PML patients, indicating that viremia occurs as would be expected for dissemination of virus to lymphoid organs and kidney, which can be monitored using qPCR assays (17, 30). Other widespread DNA-containing viruses such as cytomegalovirus (CMV) and human herpesvirus 6 (HHV-6) also demonstrate viremia in the normal population that may exceed 5% (35). CMV also latently infects CD34+ cells in the bone marrow. Because there is no animal model for PML, evidence for the tissue origins of viral latency, reactivation, and trafficking to the brain depends on studies of patients' tissues and disease progression. The cumulative evidence for the pathogenesis of JCV from the initial site of infection to the brain identifies a critical intermediary role for the immune system. Initial infection probably occurs in lymphoid cells, which may amplify infection by disseminating virus through infected lymphocytes or through viremia to other organs such as the kidney and bone marrow. The infection is then reactivated at times of immune dysfunction, which allows

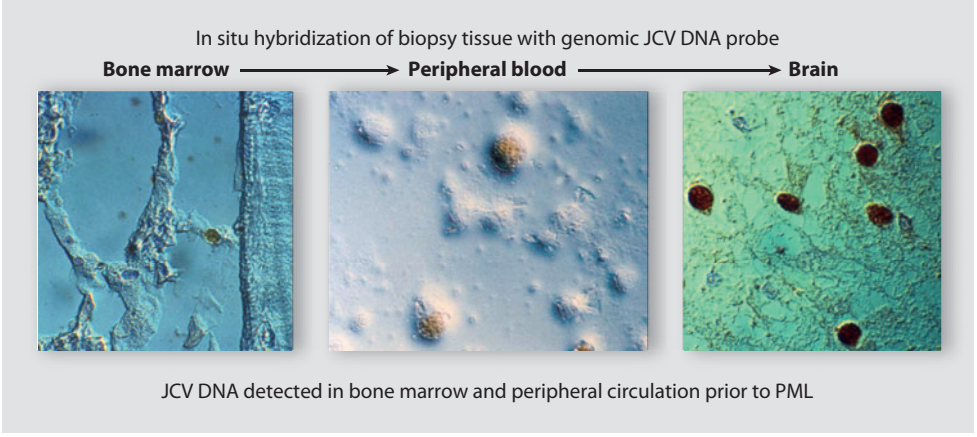

Figure 2

Suggested pathogenesis of JCV infection from latency in lymphoid tissue to infection in the brain. JCV-infected cells in fixed tissues are identified using in situ DNA hybridization with highly specific biotin-labeled, viral genomic probes and oxidation of the chromophore diaminobenzidene to a brown precipitate in the presence of hydrogen peroxide. Bone marrow tissues (*left panel*) were from biopsies of four PML patients; tissues had been taken from months to years prior to the onset of PML (average 2.3 years). In these bone marrow samples, viral DNA was detected with in situ DNA hybridization or qPCR. Viral DNA can be detected in the peripheral circulation in CD20+ cells (*middle panel*) or in plasma with qPCR. At the time of diagnosis of PML, viral DNA was detected in oligodendrocytes of biopsy or autopsy brain tissues (*right panel*). Presence of JCV DNA in bone marrow preceding PML for some time suggests bone marrow as a probable site of latency that upon reactivation could shed virus into the blood, detected as viremia, and then traffic to the brain. qPCR data are not shown.

virus to enter the brain and pass to its final target cell, the oligodendrocyte. The molecular biology of JCV also fits this model of pathogenesis, in which tonsillar stromal cells, B lymphocytes, and CD34+ hematopoietic cells all share increased expression of specific DNA-binding, transcriptional proteins that are essential for JCV multiplication (18, 36–38), unlike cells that are not susceptible to productive infection.

PML AS A CONSEQUENCE OF BIOLOGICAL THERAPIES FOR AUTOIMMUNE AND OTHER DISEASES

PML has been diagnosed periodically in patients with underlying cancers, organ transplants, sarcoid, Job's disease, Sjögren's syndrome, and other diseases but not in those with multiple sclerosis (MS), Crohn's disease, or severe psoriasis. During a global phase III clinical trial of the drug Tysabri® (natalizumab) in more than 2000 MS and 1000 Crohn's patients, PML was diagnosed in two MS patients and one Crohn's patient in 2005. Since that time, an additional 12 cases of PML have been identified, all in MS patients. The clinical history of the first patients has been well documented (39–41), as well as the evaluation of clinical histories and laboratory data on many of the other MS and Crohn's patients exposed to Tysabri (7). Currently, ~30,000 patients treated or on treatment with Tysabri are being monitored by Biogen/Idec (the company that developed and manufactures the drug) following agreements with the U.S. Food and Drug Administration (FDA), and this population includes the newly diagnosed cases of PML (42, 43). Recently PML has occurred in four plaque psoriasis patients treated with another monoclonal antibody therapy, Raptiva® (efalizumab), an incidence of ~1 in 500 cases. Approximately 57 cases of PML have occurred in patients treated with Rituxan® (rituximab), the monoclonal

antibody to the CD20 B cell marker, widely used for more than 10 years in lymphoma patients as well as some rheumatoid arthritis patients (8). Both rituximab and efalizumab are products of Genentech, Inc. Patients treated with Cell Cept (mycophenylate mofetil), a small-molecule drug that nonspecifically suppresses immune reactivity, also are at some risk for PML. The FDA has required that these drugs show a "black box" warning indicating that their use can place patients at risk for PML. The FDA also requires information on PML to be presented to patients prior to treatment. Genentech voluntarily withdrew Raptiva in April 2009 due to the risk of PML. Both the FDA and its European counterpart, the European Medicine Agency, have issued withdrawals citing the risk of PML (44).

Understanding of the potential pathogenic links between these humanized monoclonal antibodies and PML starts with their effects on functions of the immune system. Natalizumab binds α4 integrin, which may heterodimerize with integrin β1 to form α4β1 integrin (also known as VLA-4), or with integrin β7 to form α4β7 integrin; both α4β1 and α4β7 are present on T and B cells and serve as attachment ligands for VCAM (vascular cell adhesion molecules) on endothelial cells. Natalizumab prevents α4β1 binding to VCAM and α4β7 binding to MACam-1 and thus prevents T cell extravasation into the brain or gut, respectively. Because both MS and Crohn's disease feature inflammatory T cells as a significant part of the pathology, preventing access of these cells to target organs has substantial clinical effects (45, 46). Another humanized monoclonal antibody, efalizumab, binds the α1 integrin molecule CD11a on T and B cells, blocking attachment to the ICAM (intercellular adhesion molecules) on endothelial cells and infiltration into the layers of the skin (47). It is not clear what effect efalizumab has on preventing extravasation of immune cells into the brain or gut, although those organ endothelial cells also express ICAM. Efalizumab causes T cell hyporesponsiveness and downregulation of other integrin molecules, namely VLA-4 (48). Rituximab binds the CD20 receptor on B cells, initiating complement-dependent cytolysis and depletion from the peripheral circulation. **Figure 3** shows common features and general associations of these drugs with effects on the immune system. Both natalizumab and efalizumab induce a leukocytosis for weeks to months. CD4/CD8 ratios in the CSF of natalizumab-treated patients are inverted for at least six months (49, 50). The effect of efalizumab on the CNS has not been well studied.

The binding of natalizumab on integrin molecules is not limited to T and B cells. Blocking cellular adhesion molecules also prevents homing of CD34+ hematopoietic progenitor cells in the bone marrow and of pre-B cells in the marginal zones of lymph nodes (51). The same observation applies to efalizumab's blocking of LFA-1 in mouse experiments. The consequences of binding are migration of CD34+ and pre-B cells into the peripheral circulation from the bone marrow, certainly for CD34+ cells, and/or lymph nodes. This has been shown in natalizumab-treated patients within days to weeks of initiation of therapy (52, 53). In addition, gene expression analysis of peripheral lymphocytes in these patients, using genome microarray methods, showed a pattern of upregulation of several genes active in B cell differentiation (54). Similar studies of migration of cells into the peripheral circulation in patients being treated with efalizumab have not been done. However, efalizumab does downmodulate VLA-4 as well as LFA-1 (48). What do these observations have to do with the biology of JCV infection and the development of PML?

As discussed above, JCV DNA has been found in bone marrow and lymph nodes of patient months to years prior to PML onset, is found in the peripheral circulation in B cells or as free virus, can infect B cells in culture, and uses host cell factors for its genome expression. Some of the critical host factors that promote JCV synthesis are shared with genes involved in B cell differentiation that are upregulated in patients on natalizumab, members of the "Ets" transcription domain

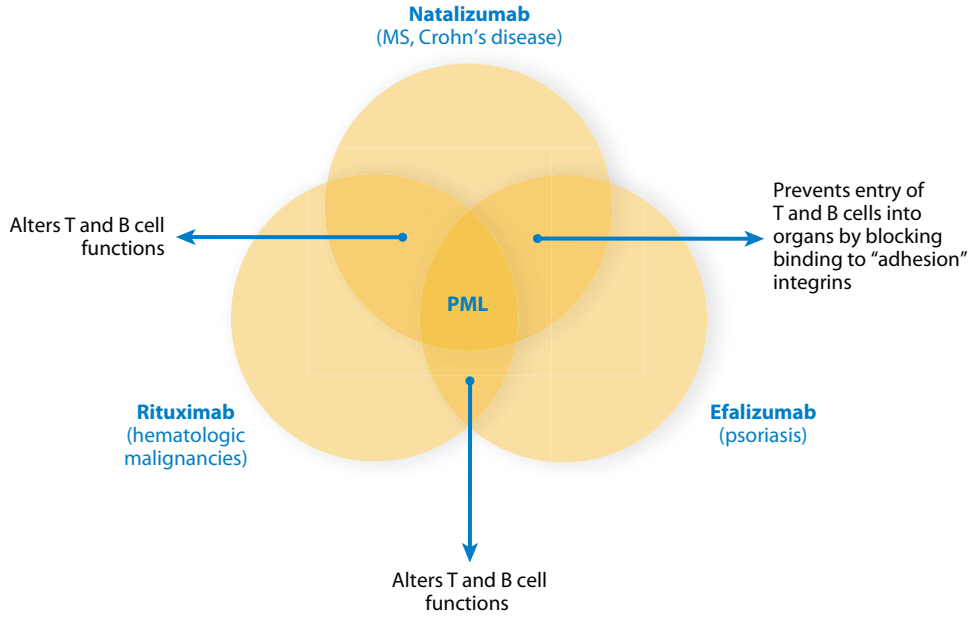

Figure 3

Humanized monoclonal antibodies for treatment of autoimmune diseases or lymphomas with a risk for PML. All three biological therapeutics alter normal immune system functions. Natalizumab is a selective adhesion molecule inhibitor that binds VLA-4, an α4 integrin that heterodimerizes with β1 and β7 integrins on T and B cells. This blocks binding to VCAM (vascular cell adhesion molecule) on endothelial cells, preventing extravasation of immune inflammatory cells into the brain (in the case of β1) or gut (β7). The drug is used for relapsing-remitting multiple sclerosis (MS) and for Crohn's disease, an inflammatory bowel disorder. Efalizumab is also an adhesion molecule inhibitor; it binds the LFA-1 or CD11a, an α1 integrin also on T and B cells, and so blocks binding to ICAM (intercellular adhesion molecule) on endothelium and keratinocytes in cutaneous tissues, preventing infiltration into the skin. Efalizumab has been used for severe cases of psoriasis. It also downregulates VLA-4 and causes T cell hyporesponsiveness. Both drugs cause a leukocytosis that may last for weeks to months. Rituximab binds to the CD20 cell surface molecule on B lymphocytes, initiating a complement-dependent cytolosis that effectively depletes the blood of B cells. It is used predominantly for treating lymphomas and leukemias but also in some cases of rheumatoid arthritis. Each therapeutic carries the risk of inducing PML, possibly owing to factors of immune modulation in addition to alterations of immune surveillance of reactivated viral infections.

family (54). One DNA binding site on the JCV promoter sequences is the SpiB binding site, essential for progression of pre B to mature B cell development and highly represented in the JCV regulatory genome (55). These data suggest a possible mechanism whereby natalizumab administration may lead to PML. In this scenario, bone marrow CD34+ and/or pre-B cells harboring latent JCV DNA migrate into the peripheral circulation owing to natalizumab blockade of their integrins to VCAM, initiation of B cell differentiation due to upregulation of appropriate genes in that pathway, and activation of JCV synthesis using the same host molecular machinery as cells differentiate into CD19/CD20 B cells (56). Virus multiplication would then take place, measured as viremia, in the peripheral circulation, and virus would enter the brain either alone or carried in B cells. Once in the brain, since immune surveillance is hampered, JCV could infect oligodendrocytes, leading to oligodendrocyte death and clinical PML. This hypothetical mechanism remains speculative at this point, but it ties together many disparate laboratory and clinical data, and serves as a testable working model. Of note,

efalizumab may act in a similar manner because it blocks integrin binding to ICAM. However, the mechanism of rituximab-associated PML is likely to be different. By depleting the peripheral circulation of B cells, rituximab may cause the B-precursors or pre-B cells in lymph nodes, spleen, and bone marrow to continually function to replace the population. It may be that under rare circumstances rituximab fails to eliminate some of those B cells that if latently infected could traffic to the brain and initiate infection in the oligodendrocyte. This might happen only rarely and require a combination of events including latent infection in pre-B cells, failure of rituximab to eliminate these cells (perhaps not yet expressing the CD20 marker), and entry of virus-carrying B cells into the brain.

The loss of immune surveillance inherent in these therapies may be another factor in the development of PML but is perhaps more relevant for other viral, bacterial, and fungal infections associated with the use of these therapies (57). In natalizumab-treated MS patients, the observation that CD4+/CD8+ ratios in the CSF six months after cessation of drug were inverted, and at lower levels than in non-treated MS patients, indicated that immune reactivity can be impaired in the CNS as expected (49).

CONCLUSION

Investigations continue into the association of PML with immune-modulating monoclonal antibody therapies as more cases are diagnosed. However, PML remains a relatively rare disease, even in patients with substantial immune suppression or modulation, other than those with AIDS. Why some patients develop PML while most do not may be related to a series of factors including rare bone marrow or other sites of viral latency, effects of drugs that mobilize such cells into the periphery, host factors that predispose to viral multiplication, and trafficking of virus into the brain where it may escape a depleted or dysfunctional immune system. The identification of patients most at risk for PML remains problematic, however, since testing for viral latency is difficult.

SUMMARY POINTS

1. PML is a rare, viral-induced demyelinating disease caused by JC virus with specific tropism for glial cells in the brain. Some populations of B lymphocytes and CD34+ progenitors share molecular factors for viral gene expression.
2. Virus can be reactivated from sites of latency in lymphoid tissues. Reactivation leads to PML under conditions of immune suppression, as in patients with HIV-1 infection, those undergoing chemotherapy for graft protection, or those receiving therapies that alter immune functions (such as monoclonal antibodies that target adhesion molecules or cause lysis of B cells).
3. The suggested pathogenesis of JCV involves mobilization of latently infected lymphoid cells from bone marrow or lymphoid tissues into the peripheral circulation, upregulation of DNA binding proteins for transcription in infected cells, and trafficking of virus into the brain.

FUTURE ISSUES

1. Identification of "functional" sites of latency, i.e., tissues that harbor JCV that are affected by immune dysfunction.

2. Development of treatments for PML, including as drugs to block JCV replication, and vaccines that augment cell-mediated immune responses. Either drugs or vaccines might be used prophylactically or therapeutically at the earliest suspicion or diagnosis of PML.
3. Directed efforts of clinical and basic research on the effect of therapies that alter immune functions and induce viral reactivation. Development of qPCR "panel assay(s)" that would identify an emerging or re-emerging virus infection following initiation of treatment.
4. Identification of host risk factors and potential sentinel biomarkers. Because of the low incidence of PML, studies of genetic predisposition may be difficult. However, analysis of T cell–mediated immune responsiveness to JCV infection, presence of viremia, and levels of expression of transcription factors essential for JCV could be done prior to initiation of therapies with known risk of PML, and periodically during the course of treatment.

DISCLOSURE STATEMENT

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57. Discusses the incidence of a number of infectious agents identified in MS patients on treatments that suppress T and B cell functions.

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Errata

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