Focus

Does the Flap of a Butterfly's Wings in Brazil set off a Tornado in Texas? – The JC Virus Story in Multiple Sclerosis

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Recently, an international clinical trial in multiple sclerosis patients using natalizumab (Tysabri®), in combination with interferon beta-1a (Avonex®), was stopped by the sponsor Biogen Idec, due to two serious adverse events, one of them fatal. These events involved two MS patients who, under treatment with natalizumab and Avonex, developed progressive multifocal leuko-encephalopathy. In addition, a third patient with Crohn's disease, who was treated for a few years with azathio-prine and received eight doses of natalizumab during a clinical trial, died. Initially, the cause of death was reported as malignant astrocytoma but due to the U.S. Food and Drug Administration's safety review, the case was reassessed and the diagnosis of PML was established.

Natalizumab, recently approved by the FDA for the treatment of relapsing-remitting MS, is a humanized monoclonal antibody that attaches to alpha-4-integrin on T cells and inhibits their interaction with the complementary endothelial receptor vascular cell adhesion molecule-1 [Figure 1]. Thus, the antibody interferes with T lymphocyte transmigration into the central nervous system and eventually reduces the damage that T cells inflict in the brain [1,2]. In addition, natalizumab has the ability to block alpha-4-beta-7-integrin binding to the intestinal mucosa addressin cell adhesion molecule 1, and was tested in clinical trials for Crohn's disease.

IFNβ-1a is approved for the treatment of relapsing-remitting MS and has multiple immunomodulatory effects that result in reduced risk of disability progression, fewer exacerbations, and reduction in number and size of active brain demyelinating lesions [3]. In this
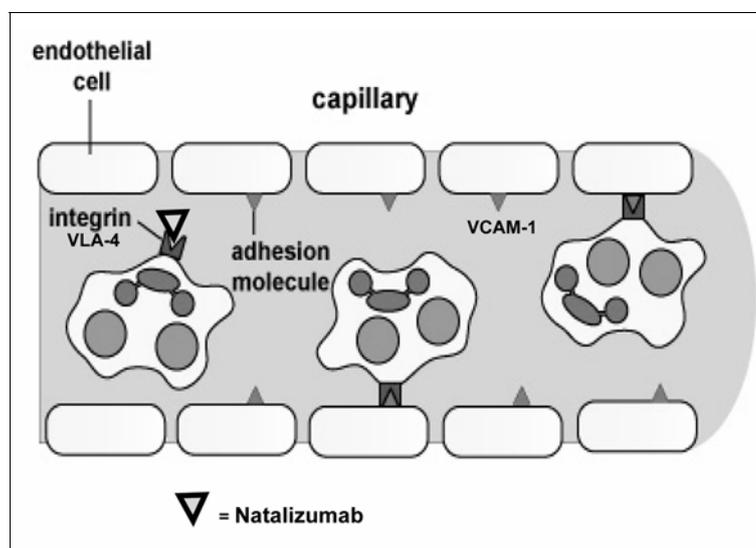

Figure 1. Mechanism of action of natalizumab (Tysabri®). To patrol the extravascular milieu, immune cells exit from blood vessels by interaction of their integrin receptors with endothelial adhesion molecules. Natalizumab binds to alpha-4-integrin (VLA-4) on T cells, inhibits their interaction with vascular cell adhesion molecule-1 (VCAM-1), and thereby interferes with cell transmigration to the target tissues.

article we briefly summarize data on JC virus and comment on PML and its relation to the Avonex and natalizumab clinical trial in MS patients.

JCV, a human polyomavirus, is a member of the Papovaviridae family, which consists of small, non-enveloped viruses with a closed circular double DNA-stranded genome. Polyomaviruses are ubiquitous in nature and can be isolated from a number of species. The human polyomaviruses were first isolated in 1971 [4]. They are named JC and BK after the initials of the patients in whom they were first discovered [5]. JCV was isolated from the brain tissue of a patient with PML. The BK virus was isolated from the urine of a

MS = multiple sclerosis
PML = multifocal leukoencephalopathy
FDA = Food and Drug Administration
IFNβ-1a = interferon beta-1a

JCV = JC virus

renal transplant patient. The two viruses are not cross-reactive serologically and serologic tests for antibodies are able to distinguish between them. JCV is widespread among humans and it is estimated that 60–80% of adults in Europe and the United States have antibodies to the virus [6,7]. Infection with JCV occurs during childhood and the virus remains in the latent state in the kidney with no apparent clinical symptoms. JCV-specific CD8+ cytotoxic T cells were found in healthy individuals and were suggested to protect against the development of PML [8]. In immunosuppressed individuals the JCV reactivation causes PML, a severe demyelinating disease of the CNS [9]. While PML was a rare disease before the AIDS pandemic, today, up to 5% of human patients infected with human immunodeficiency virus will develop PML [10,11]. How JCV is transported from sites of initial infection to the CNS remains unresolved; however, viral adherence to white blood cells and movement within the blood has been suggested [12,13], followed by entry of the virus to oligodendrocytes and astrocytes causing apoptosis, cell lysis and demyelination [14,15]. Clinically, PML is characterized by neurologic deficits that progress rapidly. The presenting symptoms include impaired cognition that progresses to dementia, cortical blindness, and hemiparesis. Less frequently there may be seizures, sensory loss and vertigo. Patients typically enter to coma, and the mortality rate is between 30 and 50% during the first 3 months [4,14,16]. Magnetic resonance imaging of the brain demonstrates multiple large demyelinating areas within the periventricular or sub-cortical white matter as hyper-intense lesions on T2-weighted scans. Usually, the lesions do not enhance with contrast on T1-weighted images following gadolinium injection. Definitive diagnosis of PML is based on pathologic examination of brain tissue. Electron microscopy, immunocytochemistry and polymerase chain reaction of viral DNA can confirm the presence of the virus. Nested PCR for JCV DNA in cerebrospinal fluid has been shown to be both highly sensitive (90–100%) and specific (92–100%) for PML [17].

No specific antiviral therapy has been proven effective for JCV. Cidofovir is being studied as a treatment option for transplant patients, and cytarabine is used in the treatment of PML, although the data regarding their efficacy are conflicting [18,19]. The two MS patients who were recently reported to develop PML were both treated with natalizumab in combination with Avonex for a period of 28 and 37 months, respectively. Both patients developed new neurologic symptoms that were initially thought to be related to their MS. The clue to the correct diagnosis of PML was the MRI findings, which disclosed extensive areas of demyelination within the brain white matter that did not enhance with contrast. Both patients were HIV-negative and their PCR testing for JCV in the cerebrospinal fluid was positive. One patient died, at the age of 46 years, within 2 months of PML onset. The third patient with Crohn's disease who died from PML received eight doses of natalizumab over 18 months and also had a history of taking multiple courses of azathioprine.

CNS = central nervous system
PCR = polymerase chain reaction
HIV = human immunodeficiency virus

Comments

This is the first time in the medical literature that PML is described in patients with MS or Crohn's disease. Taking into consideration that both MS and Crohn are autoimmune diseases but not immune compromised states, it is of major interest to understand why JCV infected, or was reactivated in these patients. An intriguing speculation is that the occurrence of PML in the above reported patients was associated with the concomitant treatment of natalizumab with either IFNβ-1a or azathioprine.

The mechanism of action of natalizumab involves inhibition of CD4 and CD8 T cell adhesion to endothelial cells [1,2]. IFNβ-1a causes an overall decrease of immune system reactivity and is known to reduce the expression of adhesion receptors, matrix metalloproteinases and chemokines, thus inhibiting the trans-migration of T lymphocytes into the CNS [20]. Similarly, the major therapeutic mechanism of azathioprine is by immunosuppression that results in down-regulation of B and T lymphocyte functions [21]. Consequently, the combination of these treatments could synergize and impair the function of CD4 and CD8 T cells, particularly the migration and surveillance in the brain. Therefore, the brain remains at least partially immunologically unprotected. This hypothesis is supported by recent reports suggesting that the control of JCV reactivation in the body involves both CD4 and CD8 lymphocytes, and a decrease in the function or number of these cells will facilitate virus replication and reactivation [10,22,23].

We therefore suggest that treatment with natalizumab and another immunomodulating drug led to a "chronic" inhibition of T cell function. This rendered the brain "immune compromised" and therefore vulnerable to PML – a process similar to what occurs in AIDS patients.

Another example of manipulation of the immune system in Crohn's disease was recently reported following the use of monoclonal anti-tumor necrosis factor antibodies. This treatment resulted in unexpected reactivation of tuberculosis, thus unmasking the protective role of TNF on the granuloma formation [24].

In conclusion, each time modern medicine maneuvers the immune system in the search for new therapies, there could also be non-desired consequences. The combination of an immunomodulatory or immunosuppressive drug with natalizumab should be avoided. Any future use of natalizumab alone for MS or other autoimmune diseases should be carefully monitored.

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TNF = tumor necrosis factor

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