**Focus**

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

Anat Achiron MD PhD,1 Shmuel Miron MD PhD1 and Yehuda Shoenfeld MD2

1Multiple Sclerosis Center, and 2Department of Medicine B and Center for Autoimmune Diseases. Sheba Medical Center, Tel Hashomer, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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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 leukoencephalopathy. In addition, a third patient with Crohn’s disease, who was treated for a few years with azathioprine 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-1 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 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.

ICV, a human polyomavirus, is a member of the Papovaviidae 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 IC and BK after the initials of the patients in whom they were first discovered [5]. ICV was isolated from the brain tissue of a patient with PML. The BK virus was isolated from the urine of a

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MS = multiple sclerosis

PML = multifocal leukoencephalopathy

FDA = Food and Drug Administration

IFNβ-1a = interferon beta-1a

ICV = JC virus

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*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.*

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renal transplant patient. The two viruses are not cross-reactive serologically and serologic tests for antibodies are able to distinguish between them. ICV 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 ICV occurs during childhood and the virus remains in the latent state in the kidney with no apparent clinical symptoms. ICV-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 ICV 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 ICV 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 ICV 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 ICV. Cidofovir is being studied as a treatment option for transplant patients, and cidofovir 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 due 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 ICV 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.

**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 ICV 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 transmigration 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 ICV reactivation in the body involves both CD4 and CD8 lymphocytes, and a decrease in the function of 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.

**References**


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CNS = central nervous system  
PCR = polymerase chain reaction  
HV = human immunodeficiency virus  
TNF = tumor necrosis factor


Correspondence: Dr. A. Achiron, Multiple Sclerosis Center, Sheba Medical Center, Tel Hashomer 52621, Israel.
Phone: (972-3) 530-3811
Fax: (972-3) 534-8186
Email: achiron@post.tau.ac.il

I'm opposed to millionaires, but it would be dangerous to offer me the position

Mark Twain (1835-1910), American novelist, whose masterpiece The Adventures of Huckleberry Finn won him international acclaim

Capsule

ECM proteins role in tumorigenesis

Patients with an inherited skin disorder called recessive dystrophic epidermolysis bullosa (RDEB) often develop squamous cell carcinoma, a form of skin cancer that is common in the general population. RDEB is caused by mutations in the gene encoding the extracellular matrix (ECM) protein collagen VII, but the role of collagen in cancer development has been unclear. Ortiz-Urda et al. show that RDEB patients who develop cancer express an aberrant, truncated version of collagen VII that confers tumorigenic properties to skin cells by enhancing their ability to invade surrounding tissue. In mice, tumor induction can be blocked by administration of antibodies targeting this collagen fragment. These results highlight the critical role of the ECM in tumorigenesis and suggest that ECM proteins may be valuable therapeutic targets for certain forms of cancer.

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Eitan Israeli