Editorial for JNV issue on PML

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A full decade has elapsed since the first three patients with natalizumab-associated PML were described in the July 28th, 2005, issue of the New England Journal of Medicine. These case reports were critical in several respects. Firstly, they highlighted that a pharmacological agent could uniquely predispose to PML as the underlying conditions being treated, multiple sclerosis and Crohn's disease, had not been previously associated with this disorder. Secondly, they raised the level of awareness of the potential risks of PML with other therapeutic agents. Thirdly, they invigorated investigations into the pathobiology of PML and the underlying causative JC virus. Although PML had been observed in approximately 5 % of AIDS patients prior to the introduction of antiretroviral therapies, until this time, it was still largely regarded as a “back of the textbook disorder,” one that typically got mentioned only in passing in medical school classes of infectious disease. Lastly, they stimulated the development of risk mitigation strategies in patients on natalizumab and increased interest in the development of preventive measures and treatments for the disorder. Therefore, it is fitting that JNV has devoted an entire issue to topics in this field.

This extremely informative issue encompasses a series of review articles by leading authorities in the field addressing a wide variety of key topics relative to PML. With respect to PML pathogenesis, Maginnis, Nelson and Atwood unravel the early stages of JCV-host cell interaction, describing the

importance of the sialic acid receptor in JCV attachment to host cells, the facilitation of cell entry by 5-hydroxytryptamine serotonin receptors, and the transportation of the virus to the endoplasmic reticulum and its disassembly. Martin and colleagues address the broad array of immune responses to JCV in PML including the humoral antibody response, oft dismissed as non-contributory to viral clearance; the importance of CD8⁺ JCV-specific T cells as effectors in eliminating JCV from the brain; and the critical role of CD4⁺ T cells.

In a paper on the potential risk of PML resulting from therapeutic agents, Chahin and Berger address the uniqueness of natalizumab among the drugs that predispose to PML. As a class 1 agent with high rates of PML, it is distinguished from class 2 and 3 agents having substantially lower risks on the basis of the latency from the time of drug initiation; the development of PML in the conditions that would not otherwise predispose to the disorder; and the relative incidence of the disorder. They also propose an expanded algorithm for managing risk with immunosuppressive agents.

Clifford provides an up-to-date review of the treatment of PML and PML-immune reconstitution syndrome. He correctly notes the absence of any firm evidence in a randomized

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control trial indicative of the antiviral effect of any of the therapies employed.

A study from Biogen investigators which mined the rich database of natalizumab associated PML cases reported to the company found that 76 % of natalizumab associated PML patients survived the illness. Factors that correlated with survival included a younger age at diagnosis, significantly lower EDSS scores, higher Karnofsky performance scales, and lower CSF JCV DNA copy numbers.

Three studies from separate groups of Italian investigators in this edition describe their experience with respect to the effect of natalizumab on JC virus. Delbue and colleagues were unable to detect JCV DNA in the blood of natalizumab treated MS patients, but detected JCV in at least one in the urine of 50 % of patients and demonstrated that over time natalizumab administration was associated with increasing levels of JCV urine shedding. They did not observe a similar effect of natalizumab administration on BKV urinary shedding. In a different Italian cohort of natalizumab treated MS patients, Pietropaolo and colleagues observed a discordance between the results of STRATIFY JCV antibody testing and JCV DNA detection in the urine at baseline analysis and imply that urinary JCV PCR may be a complementary study. They found not only JCV viremia during the second year of natalizumab treatment, but also the presence of rearranged sequences in the non-coding control region of the virus. Giannecchini and colleagues performing analyses for the presence of microRNA of JCV in the blood and urine of healthy controls and in multiple sclerosis patients before and during treatment with natalizumab, detected high

levels of JCV microRNA expression in the latter group which were consistent with the high levels of JCV DNA also detected. They suggest that the microRNA expression may contribute to the asymptomatic expression of the virus.

Koralnik and Ellis isolated JCV from the brain of a patient with JCV encephalopathy which exhibited a 143-base pair deletion in the agnogene and demonstrate that deletion of nucleotides 376–396 results in impaired expression of VP1 and infectious virion production. Wollebo and colleagues demonstrate the importance of acetylation of specific lysine residues in NF- κ B p65 activity in regulating JCV control region and activation of JCV transcription.

Two case reports of PML that grace this issue describe unusual radiographic manifestations of the disease. Spinal cord PML had been observed pathologically, but only exceptionally rarely. None of these previously reported cases exhibited clinical or radiographic features suggestive of a myelopathy premortem. In the patient reported in this edition, cervical cord lesions from PML were detected premortem. Another patient described by Spanish physicians also demonstrated unusual imaging features in which a pattern of military nodular lesions initially suggested the diagnosis of tuberculous meningoencephalitis. Lastly, a case report from Switzerland highlights the rare association of common variable immunodeficiency and PML and suggests that the combination of mirtazapine and mefloquine may have had a salutary effect on the course of the illness.

In all, this issue of JNV is full of riches regarding JCV and PML. Enjoy the read.