Review Article

Human Polyomavirus-Associated Cerebral Disorders in the Post-HAART Era

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Human polyomavirus JC is the causative agent of a deadly form of sudden onset dementia, progressive multifocal leukoencephalopathy (PML). PML is highly prevalent in immunodeficient populations, especially those undergoing chemotherapy, immunosuppressive treatments for autoimmune conditions, and HIV-1/AIDS patients. In fact, before the highly active antiretroviral therapy (HAART) regimens became available, PML was a leading cause of death in HIV-1 seropositive individuals. However, patients under HAART show increased survival times with better prognoses. In this report, we described the main differences between PML before and after the HAART era; highlighting the new patterns of presentation, the neurotropism of other human polyomaviruses, and the increased prevalence of immune reconstitution inflammatory syndrome (IRIS), as a complication of PML in patients under HAART. Lastly, we propose a revised classification of human polyomavirus-associated cerebral disorders that may reflect more accurately what clinicians encounter in their everyday practice.
patients with PML have greatly increased [11], we have recently observed noticeable changes in their patterns of presentation, which are noteworthy of being thoroughly discussed.

First, our experience mainly with Brazilian AIDS patients has recently demonstrated how prevalent PML could be as a neurological complication in HIV-1 seropositive patients, as PML cases are only exceeded by those of cerebral toxoplasmosis, cryptococcal meningoencephalitis, and CNS tuberculosis [12]. To date, the presentation of JCV-driven toxoplasmosis, cryptococcal meningoencephalitis, and CNS diseases currently constitutes a variety of syndromes recently classified as classic PML, inflammatory progressive multifocal leukoencephalopathy, JCV granule cell neuronopathy, and JCV meningitis [18]. As a result, we would like to propose a revision on the diagnostic criteria for PML as well as a complementary classification based on the number and location of the lesions (multifocal versus unifocal), and the nature of the clinical presentation—classic (subcortical white matter lesions) versus variant (involvement of the cerebellar peduncles and/or brainstem)—Figure 1(a), which may be more suitable to what practitioners encounter in their everyday practice.

Furthermore, we have noticed a growing number of cases reporting worsening of PML after introduction of HAART [19–21]. This paradoxical worsening of PML weeks or months after starting HAART is due to an uncontrolled inflammatory response of the immune system to opportunistic pathogens and to certain tumors. The so-called “immune reconstitution syndrome” or “immune restoration disease” [4], when observed in the context of PML, can lead to rapid death in the absence of intervention; however, a consensus still needs to be reached about the proper measurements to take in this scenario—Figure 1(b) [22].

Lastly, we would like to comment about the newly discovered neurotropism of BKV [23]. Although the recently characterized human polyomaviruses (KI, WU, WUV) have not yet been demonstrated to cause PML [24], there had been four cases of BKV-associated neurological compromise in AIDS patients reported in the literature; all of them accompanied by renal involvement and resulting in death [25–27]. Nevertheless, we have recently reported a case of BKV meningoencephalitis contained within the CNS, and with recovery under HAART [28]. Even when the causes of BKV neurotropism have not been established yet, we propose that this polyomavirus may be further investigated as an etiologic agent of neurological disease in AIDS patients, especially when more frequent etiologies have been discarded.

In conclusion, all the aforementioned data suggest that human polyomaviruses are playing a major role in the post-HAART era, and nothing but a multidisciplinary study of their biology and the pathogenesis of their associated diseases will lead to more efficacious interventions.

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