Peripheral Neuropathy Induced by Lopinavir-Saquinavir-Ritonavir Combination Therapy in an HIV-Infected Patient

Distal symmetrical polyneuropathy (DSPN) affects as many as 35% of patients infected with HIV.[1-2] Its etiology is complex and includes advanced immunodeficiency and HIV viremia, vitamin deficiencies (ie, vitamin B family), hormonal dysfunction (ie, thyroid), monoclonal gammopathies, and other neurotoxic events (ie, alcoholism, diabetes). Large subsets of patients develop antiretroviral-induced toxic neuropathy (ATN) while treated particularly with didanosine (ddI, Videx®), zalcitabine (ddC, Hivid®), or stavudine (d4T, Zerit®). Clinically, it is almost impossible to distinguish DSPN from ATN with the exception of exposure to nucleoside reverse transcriptase inhibitors (NRTIs). However, in the majority of patients, the exact etiology will remain unknown. Herein, we report relapse in a patient with DSPN, which we believe was caused by the use of protease inhibitor therapy.

The patient was a 40 year-old Hispanic male with a diagnosis of AIDS (CD4 count nadir of 154 cells/mm^3, HIV-RNA levels of 161 000 copies/mL [5.2 $\log_{10}$]) since 2001. He did not use alcohol, tobacco, or any other illicit drugs. His medical history was significant for development of DSPN affecting his lower extremities and both hands, 6 months after being treated with d4T, ddI, and nevirapine (NVP, Viramune®). A diagnosis of DSPN/ATN was confirmed with nerve conduction studies in 2002. His HIV-RNA level was undetectable (<50 copies/mL). The thyroid panel, blood glucose, vitamin B_{12} and folate levels, heavy metal urine screen, and erythrocyte sedimentation rate were within normal range. His rapid plasma reagin was negative. The serum protein electrophoresis did not disclose any monoclonal pattern. The patient was initially switched to zidovudine (ZDV) and lamivudine (3TC, Epivir®) and then tenofovir (TDF, Viread®) with the addition of vitamin B supplementation, L-carnitine, and gabapentin (Neurontin®), without major improvement. NRTIs were believed to be the cause of his DSPN. He was started on an NRTI-sparing regimen by using dual boosted protease inhibitors (PIs), containing lopinavir/ritonavir (LPV/r, Kaletra®) and saquinavir (SQV, Invirase®). Within 2 months of the new regimen, the patient described resolution of his DSPN. He was continued on these medications with excellent virological and immunological response (CD4 count of 450 cells/mm^{3}and HIV-RNA of <50 copies/mL). After 3 years, the patient progressively noticed the recurrence of the same symptoms, initially in his lower extremities and later in both his hands. His repeat workup again did not yield any etiology. After discussion, his ARV regimen was stopped and within 2 weeks, the patient reported a significant improvement and resolution at 4 weeks off therapy. The temporal association and resolution of the symptoms, along with negative workup, suggest that the use of dual-boosted PIs was in fact responsible for the recurrence of DSPN. There is increasing evidence that the use of PIs such as SQV and ritonavir may induce development of DSPN/ATN despite excellent virological and immunological response.[3] This may account for several cases of DSPN seen in clinical practice with undetermined etiologies.

PI-induced DSPN/ATN is not a well-recognized entity by most physicians and warrants further research as well as education for HIV practitioners.

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