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Short Communication

Severe Leukopenia Associated with Mild Hepatotoxicity in an HIV Carrier Treated with Nevirapine

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SUMMARY: Nevirapine is a non-nucleoside reverse transcriptase inhibitor used in the treatment of human immunodeficiency virus (HIV)-infected patients and in post-exposure prophylaxis. However, its use has recently been limited because of adverse cutaneous and hepatic effects. We report an HIV-infected woman who developed mild leukopenia as the first sign of a nevirapine-related adverse event, which was followed by skin and hepatic toxicity associated with a more severe leukopenia.

We report the case of a human immunodeficiency virus (HIV)-infected woman who developed mild leukopenia as the first sign of a nevirapine-related adverse event, which was followed by skin and hepatic toxicity associated with a more severe leukopenia.

Nevirapine is a non-nucleoside reverse transcriptase inhibitor widely used in the treatment of HIV-infected patients (1). However, its use is limited because of its association with relatively high rates of liver and skin adverse events (2,3).

A 38-year-old HIV-infected Caucasian woman was treated for 4 years with antiretroviral therapy consisting of zidovudine at 300 mg twice daily, lamivudine 150 mg twice daily, and with indinavir at 200 mg three times daily. Her CD4 cell count was maintained at between 150 and 200 cells/μL and she had a consistently undetectable HIV viral load. Her white blood cell (WBC) count and hepatic enzymes were within normal limits. Because of mild symptoms of lipodystrophy and with the purpose of sparing protease inhibitors, her antiretroviral therapy was changed. Thus, nevirapine, 200 mg once daily for the first 2 weeks followed by 200 mg twice daily, was substituted for indinavir, without changing her other medications.

Ten days later the patient felt well but her WBC count showed 1,530 cells/μL (normal, 4,800 - 10,000 cells/μL), with 51% neutrophils, 29% lymphocytes, 9% monocytes, and 6% eosinophils. Her hepatic enzymes were within normal limits. The patient continued to feel well, and repeated testing showed normal hepatic enzymes and higher WBC count (1,930 cells/μL). Therefore, we continued the nevirapine treatment, as we did not interpret the mild improvement of leukopenia as a possible toxic reaction to nevirapine. Two days after raising the nevirapine dose to 200 mg twice daily, the patient developed a diffuse maculopapular rash. All antiretroviral drugs, including nevirapine, were discontinued, and the patient was hospitalized. Laboratory testing showed her hepatic enzymes to be within normal limits and a WBC count of 3,800 cells/μL with 9% eosinophils. A skin biopsy of the rash showed vacuolar degeneration at the basal layer, with apoptotic keratinocytes at the malpighian layer and marked exocytosis of lymphocytes into the epidermis. Perivascular and interstitial inflammatory cell infiltrates, with numerous melanophages, were present in the dermis. These findings were interpreted as compatible with erythema multiforme-like drug eruption. The patient was treated with local and oral antipruritics, and the skin rash began to disappear. She was discharged from the hospital without resuming antiretroviral treatment and was invited for follow-up.

One week following discharge, the patient complained of generalized malaise and low-grade fever. Laboratory test results included a WBC count of 5,230 cells/μL, with 57% neutrophils, 19% lymphocytes, 8% monocytes, and 9% eosinophils; alkaline phosphatase (AP) 296 U/L (normal <115 U/L), alanine aminotransferase (ALT) 157 U/L (normal <40 U/L), aspartate aminotransferase (AST) 60 U/L (normal <40 U/L), and a normal coagulation profile. Results of serological tests for hepatitis B and C, Epstein-Barr virus, cytomegalovirus, herpesvirus, and *Mycoplasma* were negative.

Five days later, the patient returned to the clinic with persistent high-grade fever, cough, and generalized malaise. Laboratory testing showed a WBC count of 670 cells/μL, with 54% neutrophils, 27% lymphocytes, 14% monocytes, and 5% eosinophils; AP 282 U/L, ALT 221 U/L, AST 213 U/L, and a normal coagulation profile; blood cultures were negative. Bone marrow aspiration showed mild hyperplasia due to left deviation of the myeloid line, with normal cellularity of erythroid and megakaryocytic lines. No morphological signs of lymphoma, leukemia, or dysplasia of the bone marrow were noticed.

The patient was hospitalized and treated with broad-spectrum antibiotics (piperacillin-tazobactam and gentamicin) and recombinant granulocyte colony-stimulating factor (G-CSF) for 4 days. Under this treatment, her fever disappeared and her WBC count increased to 13,000 cells/μL. One month after the patient was discharged from the hospital and 2.5 months after beginning nevirapine treatment, her WBC count was 4,200 cells/μL and the hepatic enzymes had returned to normal values (Table 1).

Recently, increased reports of hepatotoxicity and skin rash

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Table 1. Clinical course

Treatment	WBC (cells/μL)	Hepatic enzyme	Fever generalized malaise	Skin rash	Nevirapine dose (mg)	Day treatment
no	6,500	normal	no	no	200	1
no	1,530	normal	no	no	200	10
no	3,800	normal	no	yes	400	17
Antibiotics, G- CSF	5,230	elevated	yes	no	no	24
Antibiotics, G- CSF	630	elevated	yes	no	no	30
Antibiotics	13,000	elevated	no	no	no	34
no	5	normal	no	no	no	50

WBC: white blood cell; G-CSF: granulocyte colony-stimulating factor.

in response to nevirapine treatment have been published in the medical literature (4,5). Indications regarding the management and avoidance have been provided by the manufacturer; we can find only one case in the literature of leukopenia developing to nevirapine (6).

In the present case, an HIV-infected woman, who presented initially with moderate leukopenia as an early sign of adverse response to nevirapine, later developed serious skin rash and hepatotoxicity and, finally, severe symptomatic leukopenia with neutropenia that resumed after G-CSF treatment. A diagnosis of sepsis was considered; however, no evidence for infection was found.Thus, we suggest close monitoring of blood counts, in addition to liver enzymes, in HIV patients during the first weeks of nevirapine treatment.

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