Nevirapine induced toxic epidermal necrolysis and non-Hodgkin lymphoma in a Human Immunodeficiency Virus positive patient

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ABSTRACT

Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI) is one of the important components of highly active antiretroviral therapy. It is sometimes associated with life-threatening adverse reactions. Here we report one such patient who developed toxic epidermal necrolysis (TEN), leucopenia and hepatotoxicity secondary to intake of nevirapine. This patient was also diagnosed to have non-Hodgkin lymphoma grade IV of anal canal for which he was given radiotherapy and two cycles of chemotherapy. The treating physicians should carefully monitor patients on NNRTI-based antiretroviral therapy so that fatalities due to adverse drug reactions can be prevented with timely intervention.

Key words: Hepatotoxicity, leucopenia, nevirapine, non-Hodgkin lymphoma, toxic epidermal necrolysis

INTRODUCTION

Nevirapine is a dipyrido-diazepinone non-nucleoside reverse transcriptase inhibitor (NNRTI). It was the first NNRTI approved by the US Food and Drug Administration for the treatment of human immunodeficiency virus (HIV) infection in 1997. Nevirapine based regimens of highly active antiretroviral therapy have been widely used in resource limited countries because of their efficacy, accessibility and comparatively low cost.[1] Nevirapine binds directly to reverse transcriptase (RT) and blocks the ribonucleic acid-dependent and deoxyribonucleic acid (DNA)-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. The activity of nevirapine does not compete with template or nucleoside triphosphates. HIV-2 RT and eukaryotic DNA polymerases (such as human DNA polymerases α, ß, γ, or δ) are not inhibited by nevirapine. The most serious toxic effects associated with nevirapine are skin reactions and liver dysfunction.[2] NNRTI viz. efavirenz, nevirapine and delavirdine exhibit a class effect with regard to cutaneous adverse reactions. The spectrum of drug rash can vary from a mild urticarial, morbilliform rash to Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).[3] HIV infection *per se* increases the risk of drug eruptions[4] including SJS and TEN.[5,6]

SJS and TEN are variants of the same spectrum presenting as severe mucosal erosions with widespread erythematous maculopapular rashes with atypical targetoid lesions. The cutaneous lesions often become confluent and show a positive Nikolsky's sign and epidermal detachment. TEN is defined by epidermal detachment greater than 30 percent of body surface area.[7]

Here we report the case of a patient infected with HIV-1 manifesting the entire spectrum of drug reactions associated with Nevirapine. Incidentally, this patient also had non-Hodgkin lymphoma (NHL) stage IV of the anal canal with lung and bone metastasis. Written informed consent was taken from the patient for collection of his data and photographs.

CASE REPORT

A 44-year-old businessman, diagnosed HIV positive 4 years ago, was started initially on zidovudine, lamivudine and efavirenz based antiretroviral

therapy (ART). Three months ago, his ART regimen was modified to tenofovir, lamivudine and efavirenz for unknown reasons. A month later, at his ART centre, efavirenz was substituted with nevirapine as he was not on antitubercular therapy. Twenty days after starting the modified regimen of tenofovir, lamivudine and nevirapine, he developed itching with maculopapular rash for which he was treated symptomatically with antihistamines and ART was continued. Fifteen days later, he presented to us with a severe maculopapular rash all over the body with targetoid lesions over the limbs [Figure 1] along with mucosal lesions in the oral and genital areas. Patient was hospitalized and ART was stopped. Over the next three days, he developed severe bullous lesions and extensive exfoliation involving more than 90 percent of the body surface [Figure 2], including the palms and soles. Oral and genital lesions were severely erosive [Figures 3 and 4] and the Nikolsky's sign was positive. Ophthalmological evaluation ruled out any eye involvement. Full-thickness epidermal necrolysis was noted on histopathological examination. Initially, all his hematologic and biochemical parameters were normal with a CD4 count of 17/cu mm. Over the next 4-5 days, he developed leucopenia of 750 cells/cu mm. His alanine aminotransferase and aspartate aminotransferase levels were 220 IU/L (N: 10-40 IU/L) and 140 IU/L (N: 10-35 IU/L), respectively. Serum alkaline phosphatase was 188 IU/L and gamma glutamyl transferase was 116 IU/L, showing 2-3 fold rise above normal. Serology for hepatitis B and C was negative. SCORTEN (score for TEN) was 3.

He was placed on fourth generation cephalosporin cefpirome 1g twice daily for 10 days. Intravenous hydrocortisone 100 mg twice daily was given for two days, changed to dexamethasone 8 mg twice daily when he started developing TEN lesions. After one week, dexamethasone was tapered to once-daily dosage over the next week and then stopped. Granulocyte colony stimulating factor Filgrastim, 5 mcg/kg was administered subcutaneously for 5 days along with adequate hydration and meticulous nursing care. Over the next 10 days, the patient's condition improved dramatically with reepithelialization of entire body surfaces except for a small erosion in the sacral region, which also healed later [Figure 5]. His CD4 count at this stage was 7/cu mm. Later, he developed lower respiratory tract infection for which linezolid was administered after culture and sensitivity reports. After one month, he recovered

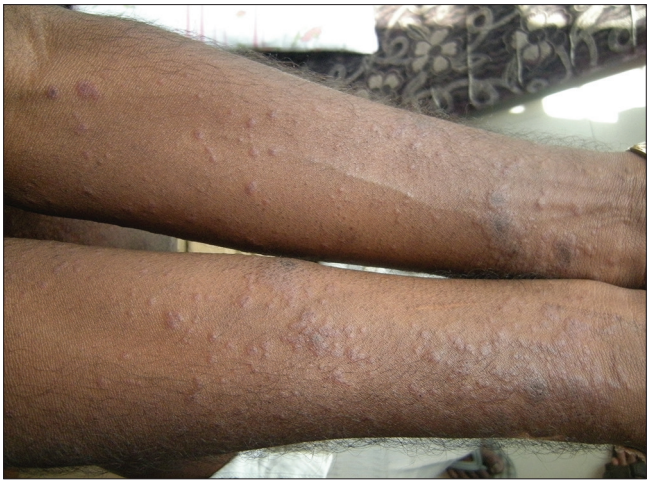

Figure 1: Targetoid lesions over the forearms as initial manifestation

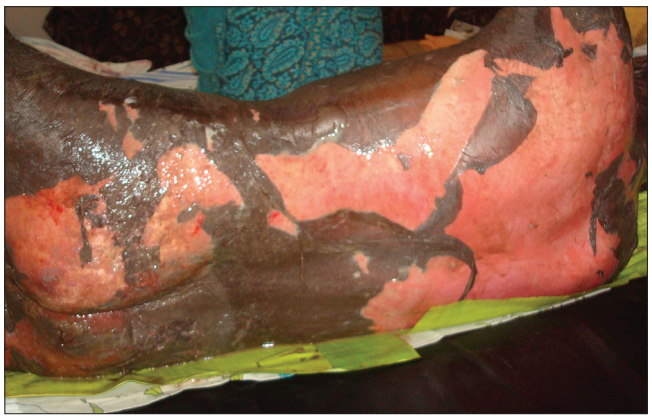

Figure 2: Epidermal necrolysis over the back

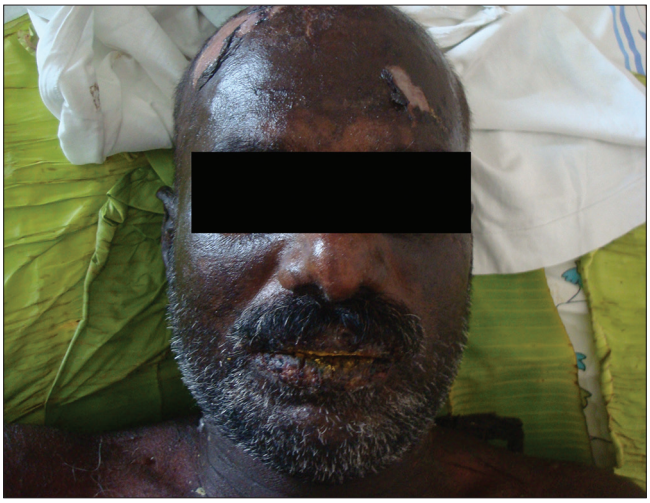

Figure 3: Epidermal necrolysis involving the oral cavity

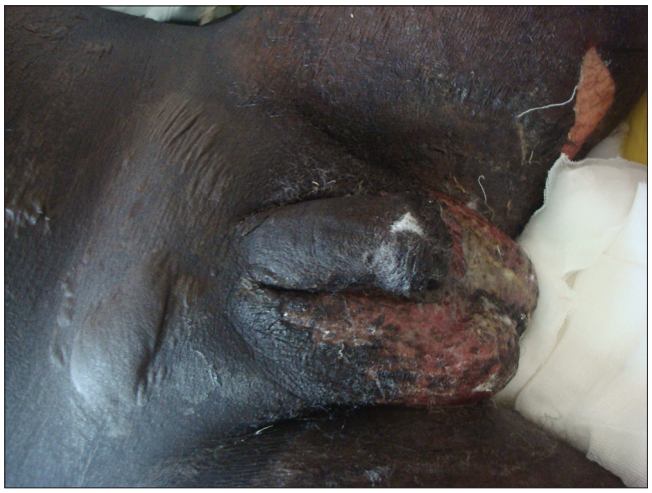

Figure 4: Genital involvement

Figure 5: Healed lesions over the back after treatment

completely and ART was restarted with tenofovir, lamivudine and efavirenz.

Two years prior, the patient was diagnosed to have NHL stage IV, of the anal canal. Biopsy had confirmed Burkitt's lymphoma. Immunohistochemistry showed features of plasmablastic lymphoma, neoplastic cells expressing Mum-1, CD138, CD56 (focal) and ki-67 (80%). He was treated with external beam radiation therapy at a dose of 40 Gy in 20 fractions to the pelvic bone and 3D conformal radiotherapy to the lung lesions. Patient was also treated with two cycles of chemotherapy with cyclophosphamide, vincristine and prednisolone. Therefore, the patient was advised follow up with his oncologist. A wholebody positron emission tomography scan showed multiple bone lesions destroying the pelvic bone with soft tissue lesions in the lungs and adrenal glands, suggesting secondary metastasis. There were also new lesions in the calvaria and left hilar lymph nodes, suggestive of progressive disease. The patient was advised admission to the oncology department for further management of his NHL and discharged on ART. He was followed up by the medicosocial worker for one month and found to tolerate the new ART regimen well.

DISCUSSION

Recent advances in treatment and modified lifestyle have prolonged the life span of HIV infected patients. But adverse drug reactions to ART continue to be a matter of concern, as they inflict significant morbidity and mortality. In our case, the patient suffered severe cutaneous adverse reaction to nevirapine, whose course and morphology varied from maculopapular rash to targetoid lesions, to extensive erosions of the skin, leading to TEN along with hepatotoxicity and leucopenia. In a study conducted by EuroScar study group on 246 SJS-TEN patients, 18 were HIV positive of whom 15 were on nevirapine. Therefore, treating physicians need to keep in mind the risk of life-threatening cutaneous reactions while prescribing nevirapine-based ART regimens.[8]

Further, our patient had NHL as a comorbidity, which must have contributed to the severity of TEN by compounding the profound immunosuppression of HIV. There have been comparative studies on the severity of TEN among HIV patients with and without comorbid malignancies. There has not been any conclusive data whether the former has any increased risk of mortality as compared to the latter.[9] Our patient not only developed TEN, but also developed hepatotoxicity and leucopenia. Thus all the known adverse reactions of nevirapine were present in our patient, which has been rarely reported. Several reports on the hepatotoxicity due to nevirapine show that the abnormalities of liver function tests are reversible upon discontinuation of the drug.[7] This happened in our patient too where the liver enzyme levels normalized four weeks after discontinuation of nevirapine.

Though TEN is associated with severe morbidity and mortality, close observation, timely intervention with meticulous nursing care and support could prevent a fatal outcome in our patient. Thus, managing HIV infection is a double edged sword the benefits of ART have to balanced against the risks of drug toxicity. A strict vigil during the initial two months of an ART regimen is mandatory to prevent such serious life-threatening reactions.

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