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Treatment challenges of nevirapine-induced Stevens-Johnson syndrome: a case report

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ABSTRACT

Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is a crucial component of antiretroviral therapy (ART) in HIV management. However, nevirapine carries a rare but potentially life-threatening risk of Stevens-Johnson syndrome (SJS). We reported a case of severe cutaneous manifestations of extensive necrolysis in an HIV-positive patient on the ARV nevirapine. This case highlights the importance of recognizing nevirapine-induced SJS, particularly in the early stages, to ensure prompt discontinuation of the drug and initiation of appropriate supportive care. Clinicians managing HIV patients on nevirapine-based ART should remain vigilant for early signs of SJS and maintain a high index of suspicion.

ABTRAK

Nevirapine merupakan suatu Nucleoside Reverse Transcriptase Inhibitor (NNRTI), NNRTI adalah komponen penting dari terapi antiretroviral (ARV) dalam penatalaksanaan HIV. Nevirapin memiliki risiko munculnya sindrom Stevens-Johnson (SJS), meskipun jarang namun berpotensi mengancam jiwa. Laporan ini menyajikan kasus manifestasi kulit yang parah berupa nekrolisis luas pada pasien HIV-positif yang mengonsumsi ARV nevirapin. Kasus ini menyoroti pentingnya mengenali SJS yang diinduksi nevirapin, khususnya pada tahap awal, untuk segera menghentikan obat dan memulai perawatan suportif yang tepat. Dokter yang menangani pasien HIV dengan terapi nevirapin harus tetap waspada terhadap tanda-tanda awal SJS.

Keywords:
anti-retroviral;
HIV;
nevirapine;
Steven-Johnson syndrome

INTRODUCTION

Nevirapine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), is one of the most commonly used drugs for HIV management. Nevirapine was first marketed in the early 1990s, and is currently FDA-approved as one of the drugs for HIV management. Nevirapine is often used in combination therapy with other types of anti-HIV drugs, namely nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine, lamivudine, abacavir, and many others. These drugs are combined with the hope of reducing the chances of the virus becoming resistant and ineffective in managing HIV.[1]

Cutaneous adverse drug reaction (cADR) is a prevalent clinical manifestation in patients with HIV/AIDS. These drug eruptions can range from mild rashes to severe blistering skin conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which occur in about 1-2 per 1000 exposed individuals and can be life-threatening.[2] Clinical features

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include morbilliform eruptions in 85.6% of cases, SJS in 8.9%, urticaria in 4.4%, and erythroderma in 1.1%. The most common drugs causing cADRs are cotrimoxazole (30%), efavirenz (28.9%), and nevirapine (16.7%).[3,4]

Clinicians should be aware that despite its rare prevalence, the potential for nevirapine to cause severe allergic reactions such as SJS must be considered.[2] In this case report, we present a case of a 30-year-old male who experienced skin manifestations after Nevirapine use.

CASE

A 30 y.o. man, diagnosed with HIV since 2020, presented with multiple pruritic rashes which appeared on the palms two weeks after transitioning from his routine ARV regimen of tenofovir, lamivudine, and dolutegravir to tenofovir (1x300 mg), lamivudine (1x300 mg), and nevirapine (2x100 mg) due to stock shortages in his area. Two days later, he developed fever, followed by the onset of crusts and blisters three days after the fever began. On clinical examination, he exhibited tachycardia with a pulse of 123 beats per min, accompanied by tachypnea and a temperature of 37.8 °C. Physical findings included periorbital edema, conjunctival injection, and crusted lesions on the lips. A maculopapular rash with a reddish base was observed on the thoracoabdominal area, with some lesions clustered together. The genitalia showed signs of erosion, and similar rashes were present on both palms and feet (FIGURE 1). We have also obtained verbal informed consent from the patient to include his clinical pictures for publication. The patient was bisexual and had been sexually active with multiple partners without using condoms. He worked as an accountant in the private sector.

Laboratory tests showed elevated AST and ALT levels, increasing from baseline values of 48 U/L and 25 U/L to 64 U/L and 104 U/L, respectively. Additionally, the patient had a decreased CD_4 cell count of 255 cells/mm³. He was diagnosed with SJS overlapping toxic epidermal necrolysis (TEN) induced by nevirapine, in the context of HIV stage 3 with oroesophageal candidiasis.

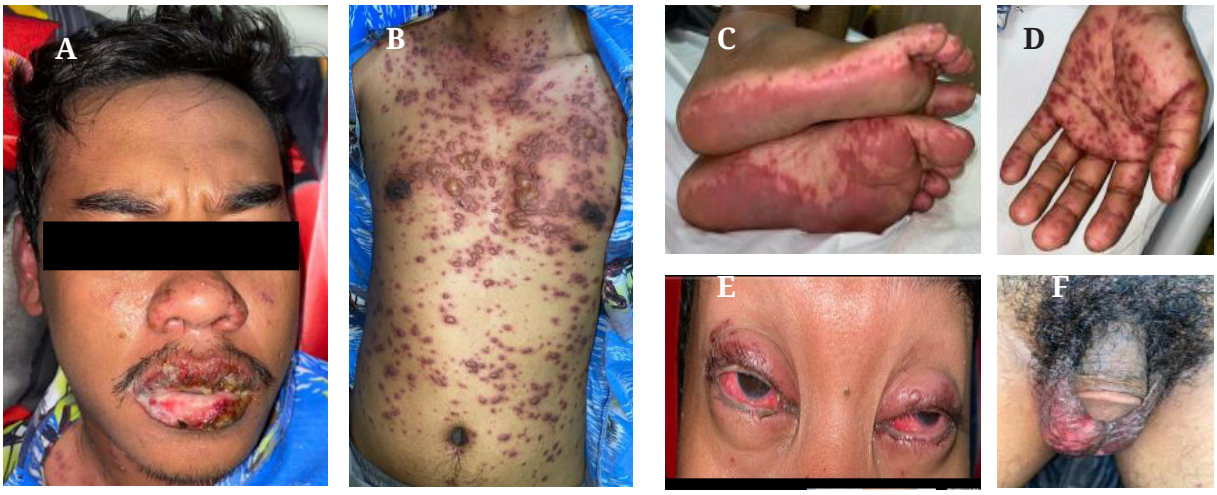

FIGURE 1. Clinical features of the patient showed erythematous rash, bullae, and erosion appearing on lips (A), trunk (B), extremities (C and D), conjunctivitis (E), and genitalia (F).

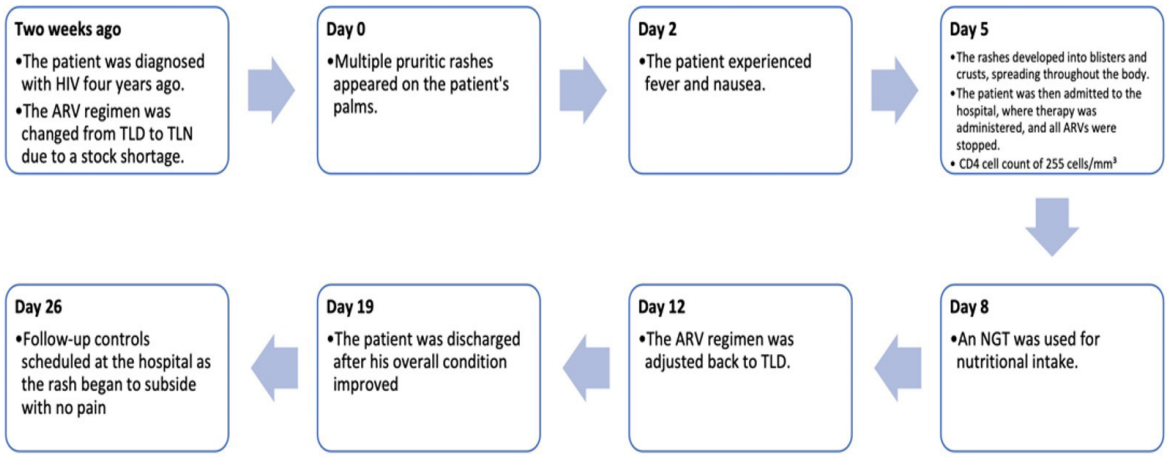

FIGURE 2. Timeline of patient's history and outcomes during hospitalization

In response, we promptly discontinued all ART, particularly nevirapine, and initiated treatment with nystatin drops for oroesophageal candidiasis. Collaboratively managed by dermatologists and ophthalmologists, the patient received methylprednisolone and diphenhydramine for systemic symptoms, along with levofloxacin eye drops and artificial tears for ocular involvement. On the 3rd d of treatment, due to difficulty swallowing, a nasogastric tube (NGT) was inserted to support nutritional intake. Hospital treatment for these symptoms lasted 14 d. Subsequently, the regimen was adjusted back to tenofovir, lamivudine, and dolutegravir. The patient was discharged to continue recovery at home, with follow-up controls scheduled at the hospital as the rash began to subside and his overall condition showed signs of improvement.

DISCUSSION

Managing HIV demands finding the right combination of drugs that balance viral suppression with manageable side effects. The fear of unpleasant and potentially harmful reactions adds to the difficulty in managing HIV. Nevirapine is a NNRTI antiretroviral drug. It is used to treat human immunodeficiency virus (HIV) infection in adults and children. Nevirapine is the most widely prescribed drug for HIV patients worldwide. Nevirapine binds directly to the reverse transcriptase (RT) and inhibits RNA-dependent and DNA-dependent DNA polymerase activity by damaging the catalytic site of the enzymes.[5]

An ADR can be defined as 'an extremely harmful or unpleasant reaction that results from an intervention associated with the use of a medicinal product; adverse events usually predict harm from future administration and require prevention, or specific treatment, or a change in dosage regimen, or product withdrawal.[6] The skin toxicity manifestation usually occurs during the first 7 - 14 d of therapy.[7]

The risk of cutaneous manifestations in patients is generally associated with higher CD_4 counts. However, a study conducted by Chateau, *et al.*[9] indicated that the mean CD_4 cell count in patients with SJS/TEN was 236.8 cells/mm³ and showed no statistical difference. It is suggested that CD_4 cell counts do not significantly influence the incidence of SJS/TEN seen in HIV patients caused by ARV use.[8,9] Additionally, it is more common in females with undetected CD_4 counts are at a higher risk of developing drug eruptions.[8] That often appear in nevirapine users are maculopapular rash (76%), urticaria (8%), SJS (4%) and angioedema (2%). In the case presented,

the patient had SJS overlapping TEN with a skin rash area of about 30%.[10]

The prevalence of TEN in the general population ranges from 0.4 to 1.2 cases per million per year, whereas in the HIV-infected population, it is significantly higher at 1000 cases per million per year.[11] Both SJS and TEN are predominantly drug-induced in at least 75% of cases.[11] Drug eruptions are considerably more common among HIV patients than in the general population, a trend associated with the use of ART.[12] Studies have shown that all classes of ART regimens can cause maculopapular exanthema and bullous drug eruptions. Identifying the specific drug causing these reactions is challenging, especially in HIV patients who are on multiple medications. Additionally, different HLA alleles can predispose individuals to various HIV-related drug hypersensitivities.[13]

Nucleoside reverse transcriptase inhibitors like zidovudine, lamivudine, and stavudine are known to cause drug hypersensitivity reactions (DRESS), mucocutaneous pigmentation, SJS, and leucocytoclastic vasculitis. Non-nucleoside reverse transcriptase inhibitors including nevirapine and efavirenz, are frequently associated with exanthematous eruptions and drug-induced toxic epidermal necrolysis (Lyell syndrome).[14] Notably, familial cases of SJS/TEN linked to nevirapine suggest a genetic predisposition.[14] In addition to nevirapine, other antiretroviral drugs such as efavirenz, zidovudine, lamivudine, and atazanavir have been implicated in cADRs, particularly maculopapular rashes.[10] On the other hand, trimethoprim-sulfamethoxazole (TMP-SMX) remains the most common cause of TEN in HIV-infected patients.[15]

HIV-infected patients experience complex immunologic changes that put these patients at higher risk of drug side effects due to hypersensitivity to drugs. In addition. Nevirapine is known to have the ability to form covalent bonds with epidermal cells, thus Nevirapine often causes skin manifestations.[16] Evidence indicates a strong genetic predisposition to cutaneous reactions with nevirapine, particularly linked to certain human leukocyte antigen (HLA) genotypes.[10] In HIV-infected Thai patients, there is a significant association between the HLA Cw* allele and nevirapine-induced rashes. Additionally, the HLA B* allele has been identified as a strong predictor for nevirapine-induced skin adverse reactions in this population. Furthermore, HLA B35 is significantly associated with nevirapine-induced skin rashes in HIV-1 antiretroviral-treated patients in India.[17]

Identifying the type of drug that causes drug eruption in patients with ARVs is difficult because monotherapy is rarely given to patients, so there are many confounding drugs. In some centers, drug re-challenge is given using the suspected drug but in this patient it is not conducted due to consideration of the severity of the patient's condition.

Another possible side effect of nevirapine is liver injury. Our patient had elevated ALT and AST levels on the 3rd d of treatment, which may still be caused by nevirapine. On subsequent follow-up, the patient's ALT and AST levels decreased to normal values after drug discontinuation. It was reported that the patient experienced improvement in ALT and AST levels at week 3-4 post discontinuation.[2] Hepatotoxicity side effects are thought to be strongly related to the metabolism of ARV drugs, especially nevirapine, which takes place in the liver.[18] *In vivo* studies in humans indicate that nevirapine is extensively metabolized by cytochrome P450 (CYP) into several hydroxylated metabolites. Furthermore, i*n vitro* studies in human liver microsomes suggest that the metabolism of nevirapine is mediated primarily by the CYP3A4 and CYP2B6 families, although other isozymes may have secondary roles.[19]

If molecular and genomic testing facilities are available, HLA can be tested. A study in China showed an association between nevirapine and the presence of the HLA-Cw*04 allele in patients who experienced hypersensitivity reactions.[20] In another study, it was also reported that patients who experienced hypersensitivity reactions are more in patients with HLAB35 findings than patients who does not have the HLA allele.[2] If adverse effects from nevirapine occur, patients are instructed to stop the medication immediately and promptly seek medical evaluation and symptomatic treatment at the healthcare facility where they received their ART. There are also some study's limitations including the inability to conduct daily follow-ups with patients after hospital discharge, caused by work-related factors and long travel distances from the patient's home to the hospital. Addressing these limitations requires future research for a more thorough understanding.

CONCLUSION

Clinicians managing HIV patients on nevirapine-based ART should remain vigilant for early signs of SJS and maintain a high index of suspicion. Patients who experience any adverse effects from nevirapine should immediately discontinue the medication and seek prompt medical evaluation and symptomatic treatment at the healthcare facility where they received their ART. Early diagnosis and intervention are crucial for improving patient outcomes and preventing complications.

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The authors declare that we have no conflict of interest to disclose.

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