Adverse Drug Reaction to Nevirapine in an Immuno-Compromised Patient: A Case Report

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Abstract

Adverse drug reaction in an immuno-compromised patient is a common condition brought about by poly-pharmacy, and notably due to the use of antiretroviral medications. We present a case of a 35 year old male, who initially presented with a morbilliform rash.. The patient was treated initially as a case of drug hypersensitivity reaction who did not respond to regular course of intravenous corticosteroid. After revealing his sero-positive human immunodeficiency virus (HIV) status, corticosteroid was discontinued and the patient responded with conservative management.

Key words: nevirapine, drug hypersensitivity reaction, adverse drug reaction

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INTRODUCTION

Cutaneous adverse drug reactions are quite common especially among patients taking multiple medication. Among immuno-compromised patients, the initiation of anti-retroviral medications and concomitant treatment of their associated diseases may compound and increase their risk of developing hypersensitivity reaction. Hence, complete history taking and adequate physical examination are important steps in the correct diagnosis and management of such patients.

CASE REPORT

A 35-year old Filipino male presented with morbilliform rash of 2 day duration. Eight weeks prior to consult, he was diagnosed to be seropositive with HIV with no medications started. At 6 weeks prior to consult, he had concomittant ill-defined, dry, slightly scaly plaques on the forehead and malar area accompanied by mild pruritus, nonspecific symptoms of cough, colds and malaise. He was started on Cotrimoxazole 800mg tab OD, Isoniazid 400mg tab OD and Clarithromycin 500mg tab BID on follow up when his CD4 count was noted to be 23cells/mm3. There were no noted lesions after starting these medications. He noted gradual progression of scaling and erythema over the next 6 weeks but claims no associated skin lesions.

At 4 weeks prior to consult, he was subsequently started on anti-retrovirals: Stavudine 40mg +Lamivudine 150mg tab twice daily and Nevirapine 200mg tab once daily for the first 2 weeks. The dose of nevirapine was then increased to twice daily on the succeeding 2 weeks. During these times, there were no noted skin lesions.

At 2 days prior to consult, the patient still had persistence of erythematous scaly plaques on the face but he claimed gradual onset of multiple and generalized, erythematous, blanching, pruritic morbilliform rash on the chest, back, arms, legs and palms and soles. This was associated with odynophagia, described as difficulty swallowing solid food, and bilateral periorbital edema. He also claimed development of undocumented fever. This was accompanied by oral ulcers. The patient had malaise, fever, associated undocumented weight-loss, weakness and odynophagia. He also claims easy fatiguability. The patient is a known diabetic since 2010 maintained on metformin. He also withheld at the time of interview that he had 2 male sexual partners in the last 5 years and practices unprotected sex. He is in a male monogamous relationship.

On examination, the patient had multiple, scattered, blanching, erythematous macules, papules and plaques on the trunk, arms and legs. Very prominent localized, ill-defined, dry, moderately erythematous patches with adherent scales on the forehead, nose, malar areas and ears were seen. He also had mild bilateral periorbital edema, with conjunctival suffusion accompanied by labial swelling and tender ulcers on the buccal mucosa (Figure 1A-C).

Upon admission, skin punch biopsy showed interface dermatitis, most probably drug hypersensitivity reaction or early erythema multiforme (Figure2). He was started on intravenous hydrocortisone 100 mg every 6 hours. We started him on a mouthwash consisting of sucralfate, diphenhydramine and aluminum chloride and twice daily 50mg intravenous diphenhydramine. After four doses of 100mg intravenous hydrocortisone were given, there was progression of lesions. It was only during this time that the patient revealed that he was previously diagnosed with HIV hence, intravenous hydrocortisone was discontinued. The patient was shifted to Levocetirizine 5mg twice daily due to persistent pruritus. Oral thrush was treated with Nystatin 5ml twice daily. Treatment of seborrheic dermatitis with ketoconazole cream and desonide cream twice daily was started. During interim, there was gradual improvement of the skin lesions. On the 6th hospital day, the patient was discharged with improvement of seborrheic dermatitis and mostly hyperpigmented patches on the body.

DISCUSSION

Adverse drug reaction (ADR) was defined by the world health organization (WHO) as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnoses or therapy of disease, or for the modification of

physiologic function" [1]. Among the manifestations of adverse drug reactions are cutaneous and are caused by immune and non-immune mechanisms [2-9]. The mechanism of drug reactions may be attributed to one or a combination of the following [10]: drug overdose, cumulative toxicity, drug interactions, exacerbation of preexisting skin disease, ecologic disturbances of skin flora, nonimmune activation of effect or pathways, metabolic changes and secondary to or side effects of the normal pharmaceutical action of the drug .

In a study conducted at the Harvard Community Health Plan involving 684 HIV infected individuals, about 8.2% of dermatologic consults showed drug-related cutaneous manifestation, while 1/3 of the admitted patients with skin diseases were being admitted due to this cause[11].

The presence of more cutaneous adverse drug reactions among HIV infected individuals may be attributed to multi-factorial theories, directly and indirectly. HIV infection may affect through active viral infection, immune dysregulation/stimulation. Indirectly, factors such as diet deficiency, co-morbidities, associated cutaneous diseases, polypharmacy, or exposure to high-risk medications may play a role for drug reactions [12]. In fact, other studies suggest that decreased CD4 count, older age, concomitant dermatologic conditions, and associated acute or reactivation Epstein-Barr virus and cytomegalovirus [13] can also contribute to the increased incidence of drug-related adverse reaction. Medications that account for drug reactions include antibiotics such as sulfonamides, sulfones and penicillin [11,13] and non-nucleoside reverse transcriptase inhibitors (NNRTI) [14]. Other explanations are regional differences in drug prescription, genetic background of patients and coexisting diseases [15, 16, 17]. Factors that may also increase the incidence of adverse drug reactions among patients taking NNRTI are female gender, CD4 cell count of less than 100 cells/ml, age above 40 years old [14]. In our case, our patient's immune status could have contributed to the development of the cutaneous drug reaction.

Typical presentation of drug reactions involving NNRTI is a rash in 10-17%, ranging from urticaria to morbillifom rash. Other lesions may show erythema multiforme major, vasculitis, exfoliative dermatitis, and photodermatitis [11]. To diagnose drug-related adverse effects, it is important to take note of the temporal relation of the symptoms to the initiation of the drug, symptomatic picture of the patient and role of history taking. Among NNRTI reactions, symptoms present within the first 6 weeks of treatment, development of rash such as morbilliform to Stevens-Johnson's syndrome and involvement of mucosal areas, and hypotoxicity together with the rash. Patients may also develop fulminant liver failure with or without systemic hypersensitivity symptoms or signs [18]. Our patient presented with morbilliform rash 2 weeks after intake of nevirapine and lamivudine. He did not have any systemic symptoms upon presentation.

A patient suspected to have an adverse drug reaction may undergo liver and renal function testing and complete blood count. For severe symptoms such as fever, urticaria, wheezing, clinical hepatitis, muscle/joint pains, desquamation, mucosal involvement, conjunctivitis, aminotransferase or aspartate aminotransferase 5 times more that the normal limit, eosinophilia, granulocytopenia or renal dysfunction warrant discontinuation of the medications. In nevirapine-associated drug hypersensitivity, screening for hepatitis B and C and normal liver function test monitoring is recommended prior to initiating treatment. A dose escalation protocol, which involves administration of nevirapine at 200mg once daily for the first 2 weeks and increase to twice daily dosing in the next 2 weeks is also advised to prevent drug reactions[18]. Our patient followed such protocol but still developed the hypersensitivity reaction.

Among patients developing adverse drug reactions, medication must be discontinued until the lesions disappear. Immediate discontinuation of the offending agent in this case was done. Our patient's non-response to corticosteroids and persistence of pruritus even after giving antihistamines may be explained by the lack of role of prednisone and antihistamines during the initial phase of the disease[19,20]. Administration of both did not prevent the further development of skin lesions in this patient.

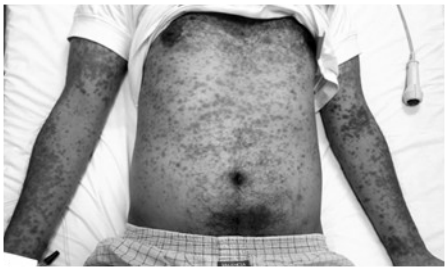

Figure 1A. Anterior trunk

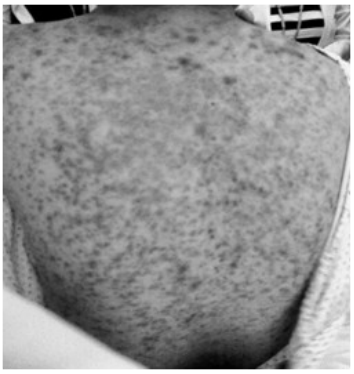

Figure 1B. Posterior trunk

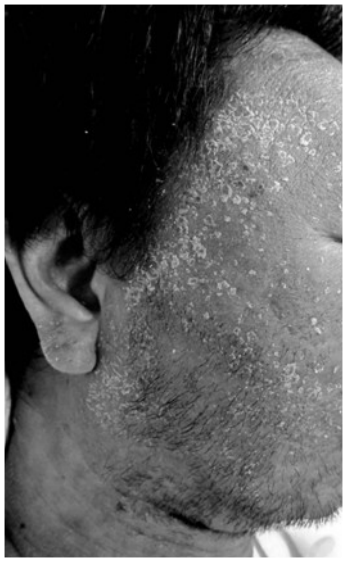

Figure 1C. Right lateral aspect of face

Figure 1(A-B). Physical exam showed multiple, scattered, blanching, erythematous macules, papules and plaques on the trunk, arms and legs. (C). Prominent localized, ill-defined, dry, moderately erythematous patches with adherent scales on the forehead, malar areas and ears.

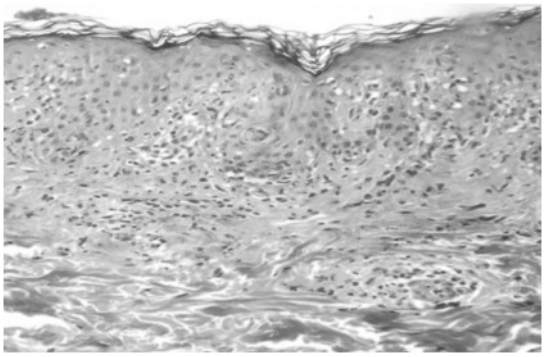

Figure 2. (HPO) Skin punch biopsy revealed basket-weave stratum corneum, spongiosis, and dermal melanophages. There were occasional necrotic keratinocytes in the epidermis with basal vacuolar alteration. Superficial perivascular to patchy band-like infiltrate of lymphocytes with eosinophils were seen in the dermis.

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