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Case Report

Efavirenz induced drug hypersensitivity reaction

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ABSTRACT

Efavirenz is the first line non-nucleoside reverse transcriptase inhibitor suggested by World Health Organization for newly diagnosed patients started on antiretroviral therapy. Dermatologic manifestations are the usual side effects associated with this drug. Authors hereby, present a case report of efavirenz induced drug hypersensitivity reported at a tertiary care hospital at Allahabad, Uttar Pradesh. The patient developed rashes and vomiting within a week of start of TLE regimen. Re-challenge test revealed confirmation of the adverse drug reaction by efavirenz. Change of the regimen was done for the patient following hospitalization for the event. This case report explains that strict pharmacovigilance is essential in the initial days of start of antiretroviral therapy. Further trials to improve the safety profile of the patients on ART are the need of the hour.

Keywords: Antiretroviral therapy, ART, Efavirenz, Hypersensitivity, HIV, Rash

INTRODUCTION

Non-Nucleotide Reverse Transcriptase Inhibitors (NNRTI) form the backbone of the Antiretroviral Therapy (ART). Efavirenz is one of the most commonly used NNRTI under the WHO guidelines.[1] It is also followed by National AIDS Control Organization (NACO) in India. However, in patients with hepatic impairment, severe renal impairment, breastfeeding, elderly who is mentally ill or with a history of substance abuse, efavirenz needs to be administered with caution.

Drug hypersensitivity reactions occur at a higher rate (i.e., 100 times higher) in patients with HIV/AIDS in comparison with general population.[2] Multiple mechanisms as immunological and metabolic factors contribute to the occurrence of hypersensitivity. The host factors and viral load also determines the severity of hypersensitivity reactions in HIV/AIDS patients. Due to multiple drug regimens in HIV/AIDS, it is highly challenging to ascribe the hypersensitivity reaction to the specific causative drug.[3]

Efavirenz hypersensitivity is commonly manifested as a mild to moderate skin rash. Severe eruptions such as SJS, TEN and erythema multiforme are also reported with Efavirenz. With its use in the first two weeks, the commonly occurred side effect is rash.

It should be discontinued if severe rash with blistering, desquamation and mucosal involvement or fever occurs. It was observed from clinical trials that 26% of patients treated with 600mg of efavirenz developed skin rash in comparison with 17% in control group. It was seen that

among 18% of patients, hypersensitivity was found to be treatment related, severe rash occurred in <1% of patients and 1.7% discontinued therapy due to rash. In 0.14% of patients, erythema multiforme or Steven Johnsons syndrome was found.[4] According to other studies, rashes and severe drug eruptions are associated with efavirenz in 4.6-20% and 0.1% cases respectively. Drug hypersensitivity with symptoms of fever, myalgia, arthralgia and elevated transaminase levels reported with the drug are extremely rare.[5,6]

Other side effects associated with efavirenz are dizziness, headache, insomnia, somnolence, abnormal dreams, fatigue, impaired concentration and they can last upto three months. Nausea, less frequently vomiting, diarrhea, hepatitis, depression, anxiety, psychosis, amnesia, ataxia, stupor, vertigo, raised serum cholesterol, raised liver enzymes and pancreatitis are also found to occur with efavirenz therapy.[4]

Through this case report, authors presented the dermatological hypersensitivity reactions occurred in a HIV patient attending ART clinic at Swarup Rani Nehru Hospital, Allahabad.

CASE REPORT

A 38 years old male patient presented to the Medicine Out-patient department with symptoms of sudden onset weight loss and nausea for three months. As per the history given, patient lost weight of 12-15kg over the period of three months following which he reached Swarup Rani Nehru Hospital, Allahabad. Investigations of the patient were done, and he was found to be HIV reactive.

The patient was a driver by profession and he has given the history of multiple hetero-sexual relationships for the past two years before the development of symptoms. He was started on tenofovir (300mg), lamivudine (300mg) and efavirenz (600mg) (TLE) regimen for his recently diagnosed HIV at ART centre attached to Swarup Rani Nehru Hospital, Allahabad. The patient was advised to take the regimen once daily at night. Mode of disease transmission in this patient was through heterosexual contact. He was in stage-1 of the disease. CD4 count at diagnosis was 194/µL.

Laboratory investigations at the start of treatment revealed as, hemoglobin-10gm/dl, total leucocyte count-12,000 cells/mm^3 with differential count of neutrophil-80%, lymphocyte-16%, monocyte-02%, eosinophil-02% and basophil-00%. Other investigations at the enrolment were, plasma glucose - 102mg/dl, serum bilirubin total-0.25mg/dl, serum alkaline phosphate (ALP)-264IU/L, serum aspartate transaminase (AST)-52.4IU/L, serum alanine aminotransferase-21.22IU/L, serum albumin 3.33gm/dl, serum globulin-3.85gm/dl, serum AG ratio-0.87:1, serum urea-48mg/dl, blood urea nitrogen (BUN)-56.45mg/dl, serum creatinine-1.78mg/dl. Serum electrolytes and lipid profile were in the normal range. Other serological markers like HbsAg and anti HCV were negative. General examination did not show any significant abnormalities. Patient developed maculopapular rashes and three episodes of vomiting after 6 days of start of ART (Figure 1). Rashes were present on the extremities, chest and trunks but did not involve the back.

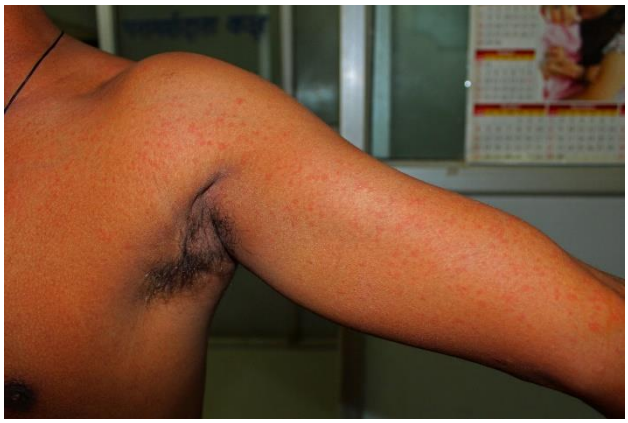

Figure 1: Maculopapular rash in the left arm and axillary region in the study participant.

Mucous membranes were not involved. Vesicles were also not present. Rashes were associated with itching and occasional pain. Patient also reported of fever and abdominal pain, the night before the development of rashes but was afebrile on examination. Vitals were stable and systemic examination was non-remarkable except for mild splenomegaly.

All laboratory parameters were within normal range except ALP and AST. Following this manifestation, drug hypersensitivity reaction was suspected, and the patient was admitted. At the time of development of symptoms, patient was not on any concomitant medications. ART was stopped and the patient was managed with intra venous fluids, oral levocetirizine and topical mometasone ointment for 1 week.

TLE re-challenge was done after a week of resolution of the symptoms under direct observation of the treating physician. Within the next 12 hours, mild symptoms reappeared and ART was abruptly stopped. Following this restart was done with fixed dose tenofovir and lamivudine and nevirapine (200mg) for 7 days and observed for symptoms.

The adverse symptoms did not reappear in the patient. Assessment by Modified Hartwig and Siegel Scale showed moderated severity. Assessment by Naranjo's criteria showed a definite association. Assessment by Modified Shummock and Thornton scale showed that the ADR was probably preventable. The patient had not reported any adverse event in the subsequent monthly follow-up visits over six months.

DISCUSSION

NNRTI are one of the most commonly used drugs in the antiretroviral regimen. Nevirapine and efavirenz are the most frequently used drugs among them. The use of nevirapine as the first line ART has reduced over time owing to higher incidence of dermatologic manifestations, most commonly skin rashes. Incidence of rashes varied from 9%-32% in the HIV positive patients.[7] Life threatening reactions like Steven Johnson syndrome and toxic epidermal necrolysis have also been reported. Serious adverse effect lead to discontinuation in around 67% of patients. Efavirenz has replaced nevirapine in the ART regime owing to its once daily dosing, better compliance and less side effects. It is preferred first line drug in ART regimen under NACO in India. It is associated with self-limiting neuropsychiatric effects, rashes, hepatotoxicity and rarely hypersensitivity reaction. Cutaneous reactions like maculopapular rashes occur in the first two weeks of initiation of the therapy. They are usually self-limiting and are rarely associated with systemic symptoms. They rarely cause treatment interruption.[8]

Efavirenz hypersensitivity commonly manifests as a mild to moderate skin rash, with rare progression to severe eruptions such as SJS and erythema multiforme being reported in 0.1% of patients, compared with 0.3-1% reported with nevirapine.[9] This patient had presented with rashes associated with systemic symptoms of fever, arthralgia and elevated liver functions. A drug induced hypersensitivity was suspected which had reduced after efavirenz was stopped, although hypersensitivity is very rare, the underlying cause is usually idiopathic.[10] Half-life of efavirenz drug usually varies from 52-76 hours.[5] The drug is mostly metabolized by CYP 2B6 pathway.[11] Delayed metabolism of the drug due to impaired liver function can be a reason for higher drug concertation in the case. A cohort study revealed that HLA-DRB1*01 is significantly associated with cutaneous hypersensitivity.[12] Drug concentration could not be measured in the current setup. Leung et al, has mentioned that higher concentration of efavirenz is observed in blacks and Latino male compare to whites. Data on Asian population is scarce.[13] Nevirapine induced hypersensitivity is mostly immune mediated with occurrence within first 3 months of starting treatment.[14] Treatment with efavirenz can be continued if the rash is not severe. Proper counselling of patient is essential. Antihistamines or topical steroids should be added to the therapy.

CONCLUSION

In the present case study, patient was suspected to be suffering from drug hypersensitivity due to efavirenz. Symptoms subsided on drug withdrawal. Since efavirenz is the most commonly used NNRTI regimen, drug toxicity identification and management are of utmost importance. Monitoring of adverse drug reactions with timely interventions can reduce the severity of symptoms. Educating the patient about the probable adverse effects timely would prevent the occurrence of severe adverse reactions.

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