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Case Study

NEVIRAPINE INDUCED STEVENS JOHNSON SYNDROME: A CASE REPORT

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ABSTRACT

Adverse drug reactions (ADRs) are one of the major reasons for morbidity and mortality in India, but they often go undetected and under reported. Nevirapine (NVP) is one of the first line agents used for anti retroviral treatment (ART) of human immunodeficiency virus (HIV) infection. It is known to cause mild skin rash among these individuals during the first weeks of therapy, however Stevens Johnsons Syndrome (SJS) is rare. Here we report afifty three-year-old HIV positive individual presenting with maculopapular rash all over the body and ulcerations of the oral and genital mucosa following administration of NVP. He was diagnosed to have SJS. The symptoms resolved completely 2 weeks after stopping the drug. Causality assessment using Naranjo and the World Health Organisation (WHO) probability scale indicated a probable relationship between the patient's symptoms and the use of NVP. Thus, clinicians should be vigilant to allow early detection of these problems, as the early diagnosis and treatment of SJS can reduce the morbidity and mortality considerably.

Keywords: Adverse drug reactions, Human immunodeficiency virus, Nevirapine, Stevens johnsons syndrome.

INTRODUCTION

Nevirapine (NVP), a potent dipyridodiazepinone non-nucleoside reverse transcriptase inhibitor (NNRTI), was the first drug of its category, available in 1997, for the treatment of human immunodeficiency virus (HIV) infection [1, 2]. According to the National AIDS Control Organisation guidelines (NACO), NVP is one of the first line drugs used for treatment of HIV. It is used as a part of combination therapy for both post exposure prophylaxis as well as part of highly active anti retroviral therapy (HAART) regimens [3]. NVP binds directly to the reverse transcriptase enzyme and blocks RNA-dependent and DNA-dependent DNA polymerase activity, thereby causing disruption of the enzyme's catalytic site [1, 2]. The common adverse drug reactions (ADRs) associated with NVP are skin rashes and hepatotoxicity. Skin rashes are usually mild and Stevens Johnsons Syndrome (SJS) is rarely seen in only about 0.5-1% cases [4]. NVP based HAART regimens have been widely prescribed in resource-restricted countries like India because of their efficacy, good tolerability, accessibility and comparatively low cost [1, 2, 4]. Herein, we report a case of SJS due to NVP based HAART regimen.

CASE REPORT

The case study below was prepared in accordance with the principles in the Declaration of Helsinki. Consent was taken from the patient on a suitably designed patient informed consent form.

A newly HIV diagnosed fifty three-year-old male patient, on HAART regimen with lamivudine (3TC), stavudine (d4T) and NVP since 1 week, presented with complaints of fever, headache, weakness, itching and extensive rash all over the body since 3 days. He also had facial and lip swelling and lesions in the oral cavity and genital mucosa associated with redness and pain. On examination, patient had fever and generalised maculopapular rashes all over the body which was bright red in colour, itchy and diffuse (fig. 1). Oral examination revealed multiple oral ulcers over the lips, labial mucosa, hard and soft palate, buccal mucosa and floor of the mouth. Haemorrhagic crusted lesions were seen on both upper and lower lips (fig. 2). Ulceration of the genitalia was also noted. All hemotological and biochemical parameters were in normal limits, with a CD4 count of 0.00011 cells/l (110 cells/mm^3). SJS was diagnosed based on his history and clinical presentation. NVP, 3TC and d4T were stopped immediately and the patient was managed conservatively with cold sponging and oral antihistaminic cetirizine 10 mg once daily. There was gradual improvement in patient's condition over the next 1 week and lesions completely disappeared after 2 weeks. Re challenge with NVP was not performed due to ethical constraints, but a modified HAART regimen was started that included efavirenz (EFV) in place of NVP. Causality assessment was done using Naranjo's criteria and the World Health Organisation (WHO) probability scale and this case of SJS recorded a probable association between the reaction and drug intake (Naranjo score 6).

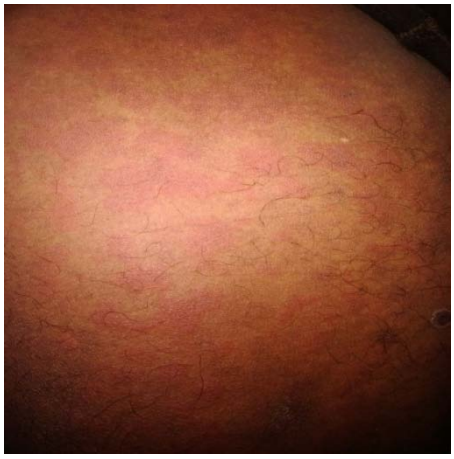

Fig. 1: Maculopapular rash over the body

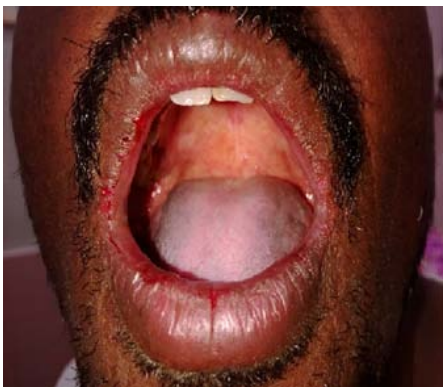

Fig. 2: Haemorrhagic ulcerations of mucosal surface of oral cavity

DISCUSSION

SJS is an immune complex hypersensitivity reaction characterized by extensive necrosis and detachment of the epidermis and erosions of mucous membrane [3, 4]. Studies reveal that the mechanism involved in drug induced SJS is neither dose-independent nor associated with alterations in the CYP450 enzyme system but is more likely due to hypersensitivity reactions in which drugs act as antigen and induce T cell mediated immune response in genetically susceptible individuals. Individuals with antigens like HLA Bw44, HLA-B12 and HLADQB1 * 0601 appear to be more prone to develop SJS. Granulysin, a cationic cytolytic protein released primarily by cytotoxic T cells (CTLs) and natural killer (NK) cells, is considered a key mediator responsible for the disseminated keratinocyte death and tissue damage, thereby producing the unique clinical presentation of SJS [5].

SJS can be caused by various factors like infections, malignancies however drugs are implicated as the major causative agent [3, 6, 7]. Studies report that most cases of SJS in HIV patients were due to antibacterial sulphonamides in western countries and thiacetazone in Africa [6]. In our patient, the development of mucocutaneous lesions had a temporal relationship with administration of NVP as an interval of 4-28 days between initiation of drug use and on set of the reaction is highly suggestive of an association between the drug and SJS [5]. Moreover the signs and symptoms were most consistent with NVP induced SJS, so we believe that NVP was responsible for the SJS in this patient. Other drugs like 3TC and d4T can be excluded as there is no obvious association with SJS [2] and no reaction was observed when they were re challenged. Known risk factors for SJS include female gender, previous history of drug allergy, low body weight, high NVP plasma concentration and CD4 counts>0.00025 cells/l (250 cells/mm3) in women and>0.0004 cells/l (400 cells/mm3)in men [7]. While our patient had a low CD4cell count of 0.00011 cells/l (110 cells/mm3), he was average build and had no previous history of drug allergy. Moreover, HIV-infected patients are at higher risk of developing SJS because of decreased anti-oxidant levels due to infection. In addition, the greater likelihood of using high doses of drugs by these patients, further predisposes them to SJS [7].

The initial skin lesions in SJS are usually erythematous, irregularly shaped purpuric macules which progressively coalesce followed by necrosis and detachment [3-5]. It mainly involves the face, trunk and proximal limbs [3, 5]. Mucous membrane involvement of at least two sites is seen in approximately 90% of cases, before or following skin eruption [3, 4]. SJS is also associated with extra cutaneous symptoms like fever, pain, weakness etc. [3]. Our patient had red and itchy maculopapular rashes all over the body, painful ulcerations and haemorrhagic lesions involving the oral cavity and genitala along with extra cutaneous symptoms like fever, weakness and headache. Investigations usually involve a complete blood count. This may be normal but a significantly elevated count indicates superimposed infection [6]. In our patient the counts were normal denoting any underlying infection was less likely. SJS has high morbidity and is potentially life-threatening. Mortality rates are estimated to be approximately 5% [4]. Treatment includes prompt recognition and withdrawal of suspected drugs and hospitalization [3, 5]. Management primarily involves supportive and symptomatic care [4]. Because of the role of immunologic and cytotoxic mechanisms in the development of SJS, a large number of immunosuppressive and anti-inflammatory therapies have been used to prevent the progression of the disease [3]. However, management in our patient involved with drawal of the offending agent and conservative care with oral antihistaminics as no specific signs of infection were identified.

Anti retroviral treatment (ART) is becoming increasingly complex [2, 5]. Close monitoring and follow-up of patients placed on NVP is important not only to improve adherence, hence efficacy but also to prevent the development of severe complications such as SJS. One must suspect SJS, if a patient on NVP, presents with symptoms such as irritation of the skin and mucous membranes [5].

CONCLUSION

Necessary precautions must be taken while introducing NVP in any HIV patients. It is necessary to keep them under strict observation for the first few months following the start of treatment with NVP. It is also important to forewarn them about such possible reactions and the importance of seeking medical help immediately if any skin reactions develop. Moreover, it may be appropriate to start NVP as lead dose to sensitize the immune system gradually and to avoid serious ADRs. This may help prevent life threatening reactions and at the same time may prevent non adherence to treatment. This case report also tends to highlight the role of genetic determination of individuals susceptible to such ADRs and the use of personalised medicine in the management of HIV.

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CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest that are directly relevant to the content of the case report.

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