Case Report

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Stevens Johnson Syndrome Induced by Nevirapine in Haart Regimen: A Report of Three Cases

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ABSTRACT

Background: Adverse drug reaction is a critical public health issue in treatment adherence and retention. Antiretroviral therapy has been effective in reducing the morbidity and mortality in Human Immunodeficiency Virus infected individuals. Nevirapine, one of the components of antiretroviral therapy is widely prescribed because of its efficacy and tolerability. The risk of mucocutaneous adverse reactions associated with nevirapine in Human immune deficiency virus may vary from mild rashes to Stevens Johnson syndrome/Toxic Epidermal Necrolysis. Here, we report three cases of Stevens Johnson syndrome associated with nevirapine in Highly Active Antiretroviral Therapy.

Keywords: adverse drug reactions, Highly Anti Retroviral therapy, nevirapine, Stevens Johnson syndrome.

INTRODUCTION

Adverse drug effects occur frequently and have been a public health concern. Severe cutaneous adverse reactions to drugs are among the most frequent complications of the therapy owing to its high morbidity and mortality.[1] Nevirapine (NVP) based regimens are commonly used Highly Active Antiretroviral Therapy (HAART) regimens for the treatment of HIV infection in National Aids Control Organization.[2] NVP is a dipyridodiazipinone - non nucleoside reverse transcriptase inhibitor used to treat Human Immuno deficiency Virus (HIV) infection.[3]Even though out of its effective therapeutic outcome it has certain side effects like skin rashes, nausea, headache, fever, rise in liver enzymes and hepatotoxicity.[2, 4] Its occurrence is accounted in 0.5 – 1% cases[3]. One of the undesirable side effects of HAART in HIV management is Stevens Johnson Syndrome (SJS). It is a potential deadly skin disease that usually results from a drug reaction in which symptoms may occur within hours to weeks of exposure due to triggering agent. We report three patients who were on NVP based HAART regimen for HIV infection and had developed SJS.

CASE REPORT 1

A 32 years old female patient reported to the hospital with a complaint of ulceration of lips and generalised papular eruptions on the face, arms and hands from two weeks. She had no previous history of drug allergy. The patient was HIV positive diagnosed and was on HAART regimen from one month. There was gradual onset of lesions after one week since the initiation of the therapy. On clinical examination, generalised multiple erythematous plaques, papules and target lesions were seen on the extremities, body and face (Fig 1) On some parts of the face, the skin was denuded and had pigmented crusted appearance. On oral examination, there were multiple ulcers on the labial mucosa, tongue and floor of mouth. Ulceration and hemorrhagic crusting was seen on the mucosa

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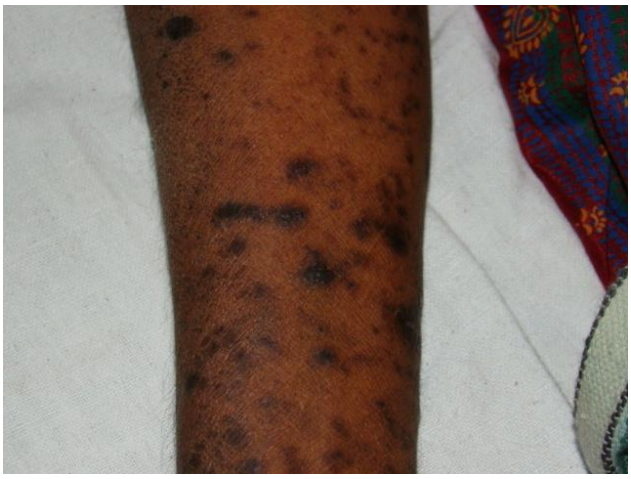

Fig 1: Target lesions seen on the hands

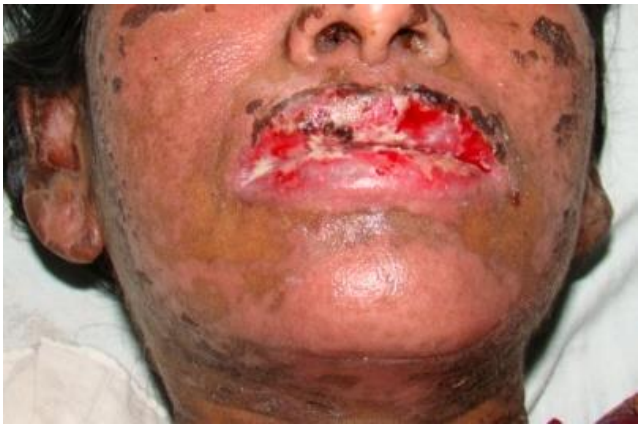

Fig 2: Ulceration of the nares and lips with haemorrhagic crusting.

Fig 3: Ulceration of the nares, oral mucosa, lips with hemorrhagic crusting.

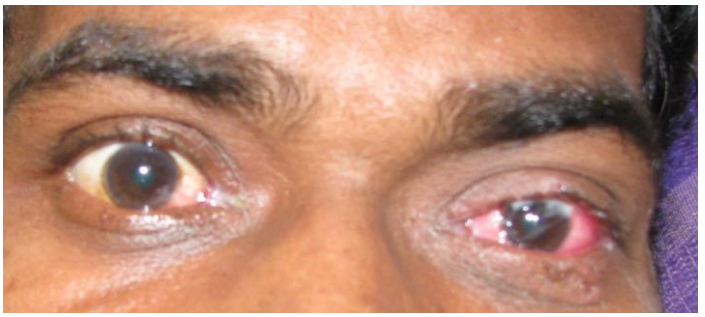

Fig 4: Ulceration of conjunctiva on left eye.

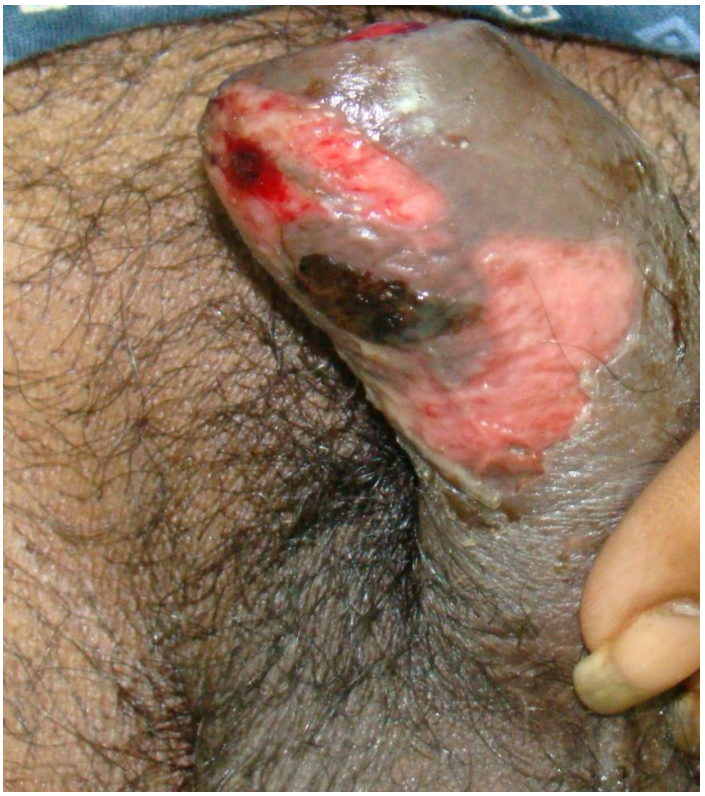

Fig 5: Genital ulcers.

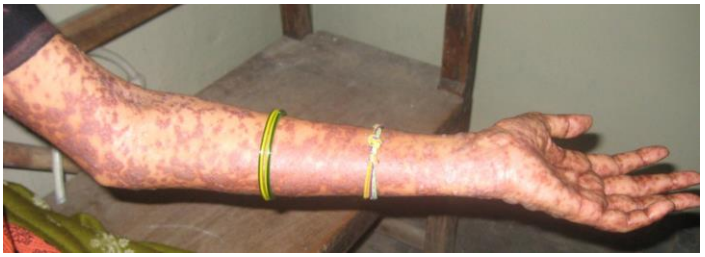

Fig 6: Generalised erythematous maculopapular and target lesions on hands.

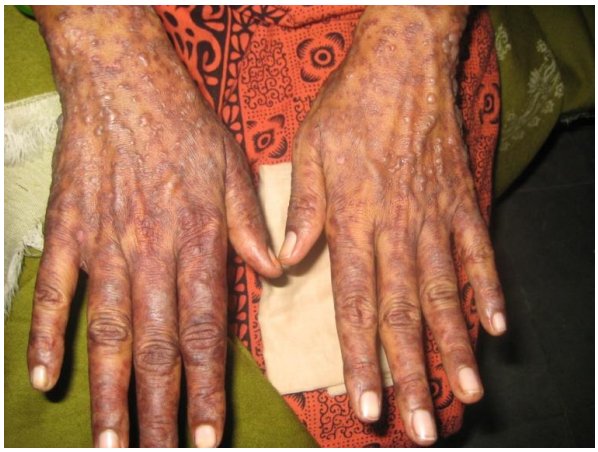

Fig 7: Macular lesions with vesicles on the hands.

of nares and lips. (Fig 2) The conjunctiva and the genital mucosa appeared normal. On laboratory investigations, the CD4 count was less than 100 cells/ul, but the Hb% and Erythrocyte Sedimentation Rate (ESR) were altered. The liver enzymes appeared normal. Based on the history and clinical presentation, a diagnosis of SJS was given.

CASE REPORT 2

A HIV positive diagnosed 40 years old male patient on NVP based HAART regimen presented with a complaint of ulceration and burning sensation of the lips since ten days. He was diagnosed HIV positive six months back and was on HAART regimen from one month. He had no previous history of drug allergy. On clinical examination, there were generalised multiple erythematous plaques on the face and body. The extremities showed pigmented plaques. On oral examination, there were multiple large ulcers in all the areas of the oral cavity and lips (Fig 3). On ophthalmic examination, revealed conjunctivitis on the left eye (Fig 4). Genital ulcers were also observed. (Fig 5) On investigations, The CD4 count was below normal limits and the total blood count was normal. Based on history and clinical presentation, SJS was diagnosed.

CASE REPORT 3

A 28 years old female patient diagnosed HIV positive and on HAART regimen presented with fever and itchy rashes on face, arms and hands from two weeks. He had no reported history of drug allergy. On examination, she had multiple erythematous maculopapular and target lesions on the face, hands and arms. (Fig 6) Some areas showed vesicles along with the plaques on the hands. (Fig 7). The mucosal regions appeared normal. On investigations, the CD4 count appeared less than normal. The liver enzymes were in normal limits.

DISCUSSION

In 1922, Steven and Johnson first described SJS, as an immune complex hypersensitivity reaction that can be caused by many factors such as infections, drugs, vaccinations, systemic diseases, physical agents, foods and malignancies.[5,6] SJS is characterized by sloughing of the skin and mucous membranes at the dermal epidermal junction. The most lethal cases may affect the internal organ systems, with necrosis of gastrointestinal and respiratory tract mucosae.[7] Drugs are an important cause of Stevens–Johnson syndrome, but infections or a combination of infections and drugs has also been implicated [8] The drugs that cause SJS commonly are antibacterials (sulfonamides), anticonvulsants (phenytoin, phenobarbital, carbamazepine), non-steroidal anti-inflammatory drugs (oxicam derivatives) and oxide inhibitors (allopurinol).[6] The link between systemic hypersensitivity reactions and nevirapine has been well documented.[4, 9, 10] An immunological response involving CD8+ T lymphocytes is the most likely explanation for the pathogenesis of SJS/TEN. Other potential factors are the causative drug's inherent properties or chemical structure, patient factors such as HIV status and CD4+ count, ethnic background, age and gender[9]

SJS effects all ages and both the genders. It is characterized by cutaneous lesions which are erythematous macules that rapidly develop central necrosis with papules, bullae and denudation on face, trunk and extremities. Cutaneous sensitivity associated rash with NVP occurs within first four weeks of therapy.[6] In all our three cases reported here showed mucocutaneous lesions within two weeks of initiation of the NVP in HAART regimen, generalised erythematous popular lesions, target lesions on the body, extremities and face. One of our case also presented with vesicles along with the lesions on the hand.

Mucosal eruptions typically occur on conjunctivae, mucous membranes of nares, mouth,

anorectal junctions, vulvovaginal and urethral meatus[2]. Ocular involvement having conjunctivitis was observed in one of our patient and had developed within ten days of initiation of therapy. Similar findings were reported in a case report by V L Lamani et al and Metyr et al [2,11] Oral adverse effects observed due to nevirapine are irregular ulcerations with blood encrustations on lip, stomatitis and irregular erythematous ulcers on oral mucosa [12, 13] The two cases out of three we reported here experienced oral ulcers with burning sensation and ulcerations on the lip with hemmorhagic encrustations. Oral lesions usually predate the cutaneous manifestions.[6] Genital ulcerations were also observed in one of our reported case.

Systemically, the gastrointestinal symptoms associated with NVP may manifest as dysphagia, dyspepsia, and bloody diarrhea. Myocardial injury and hematological complications have also been reported[6]. These findings were not observed in any of our reported cases. Manifestation of hepatic toxicity may range from reversible mild to moderate elevation in Liver enzymes to fulminate hepatic failure.[2] In our cases, the liver enzymes were within normal range. Other clinical features may include pneumonitis, productive cough, fever, headache and malaise [2,14]

Some studies report that most cases of SJS in HIV patients were due to antibacterial sulphonamides[2]. In our patients, 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 onset of the reaction is highly suggestive of an association between the drug and SJS. Moreover the signs and symptoms were most consistent with NVP induced SJS, so we believe that NVP was responsible for the SJS in our patients.

Prompt diagnosis, identification of, and early withdrawal of all suspect drugs are the most important preliminaries. The first line of management is the immediate withdrawal of the HAART and systemically managed with corticosteroids followed by symptomatic care. Oral ulcers are treated with topical anaesthetic gels to relieve from pain. After healing, follow-up is needed for ophthalmologic and mucous membrane sequelae. Treatment also includes volume replacement, optimization of electrolyte balance and glycemia, aggressive nutritional support, pulmonary care, and prevention and treatment of infections. [15] World Health Organization (WHO) guidelines recommend initiation of ART with efavirenz, the only alternative NNRTI available that has similar efficacy to NVP, but a different toxicity profile.[6] In all of our cases, HAART regimen was withdrawn and dexamethasone was administered. IV fluids, topical application of betamethasone cream for lesions, topical lignocaine gel for oral ulcers, chlorhexidine moutwashes, anti allergic drugs were advised. After complete resolution of all the symptoms, HAART regimen was restarted with efavirenz by replacing NVP and showed positive outcome.

CONCLUSION

The cases presented here bear important clinical messages. Necessary precautions must be taken while introducing NVP in any HIV seropositive patients. It is necessary to keep them under increased clinical vigilance 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. Although antiretroviral therapy is potent from antiviral perspective, they often have pervasive threat due to patient non adherence.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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