Nevirapine Induced Stevens-Johnson Syndrome (S-J Syndrome) with Ocular Complication in a HIV Positive Patient

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ABSTRACT

Stevens - Johnson syndrome has been reported in 0.3% of patients taking Nevirapine as non nucleoside reverse transcriptase inhibitor in the Highly Active Anti- Retroviral Therapy within first four to six weeks of treatment. We report one such uncommon case in a young adolescent HIV infected male who developed generalized skin eruptions with mucous membrane involvement of genitalia, oral cavity and conjunctiva of Eye after one week of escalating dose of Nevirapine (200mg twice daily) following lead- in period of 14 days (200mg once daily) . There was improvement and healing of skin, mucous membrane and ocular lesions with aggressive management but developed chronic ocular complication in the form of symblepharon of both eyes on six month follow up. This case is reported to create awareness towards Nevirapine induced adverse drug reaction and recommend to withdraw Nevirapine if any cutaneous eruption occurs during first month of treatment as the mortality in moderate to severe cases of Stevens-Johnson Syndrome is around 30%.

Keywords: HIV, Stevens- Johnsons Syndrome, Nevirapine, Ocular Complications

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INTRODUCTION

Stevens- Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are acute conditions and is characterized by skin blisters and erosion of mucous membrane. Incidence rates of SJS and TEN are approximately 1 to 7 cases and 0.4 to 1.2 cases per one million people respectively per year.[1-5] The incidences of TEN and drug reaction are higher in HIV, SLE and bone

marrow transplant recipients.[6] Cutaneous involvement ranges from mild erythematous macules to extensive epidermal detachment. The International classification of SJS/ TEN is based on the body surface area of involvement (BSA). SJS involves less than 10% BSA; TEN involves more than 30% BSA and there is an overlap in definitions with involvement of 10 to 30% BSA.[7] Etiologic factors identified in pathogenesis of SJS are usually categorized as iatrogenic, infections or idiopathic.[8,9]

Numerous drugs implicated as iatrogenic cause of SJS are several Anti-Tuberculosis drugs,[10] Aromatic anti convulsants [eg. Carbamazepine, Phenobarbitol and Phenytoin], Anti-Inflammatory drugs, Anti- Infective drugs [eg. Aminopenicillins, Sulfonamides, Quinolones, Cycline anti biotics] [11,12] and Anti- Retroviral (HAART) medications [eg. Nevirapine, Indinavir, Didanosine].[11] HIV infected patients have higher predisposition to the condition because of decreased antioxidant levels owing to the infection.[13,14]

The persistence of high risk of SJS or TEN in relation to HIV infection is currently associated with exposure to Nevirapine.[15] The mortality rate of SJS and TEN is high and even in moderately severe cases could be as high as 30%.[16] Most Patients with SJS or TEN has prodromal symptoms of fever , headache, myalgia and thereafter developing erythematous maculo papular skin lesions appearing first on face and upper part of trunk, proximal part of extremities with spread rapidly to rest of the body. Mucous membrane is always involved in SJS and TEN in more than one sites such as buccal, ocular and genitial mucosa.

More than 80% of patients have Ocular involvement such as purulent conjunctivitis and can have complications from chronic conjunctivitis to complete blindness. Multisystem involvement in severe cases can occur involving gastro intestinal and respiratory systems.[17] All suspected cases of SJS or TEN is confirmed by skin biopsy for histologic and immunofluorescence examination which shows supra basal layer apoptotic keratinocytes in early stages and later lesions has full thickness epidermal necrosis with separation of epidermis from dermis.

Treatment of SJS although requires minimal drug therapy but early aggressive management is necessary. Treatment includes management of pain and fluid loss, supportive care of respiratory and ocular complication, maintenance of adequate nutrition, prevention of gastrointestinal ulcer and psychological support to the patient.

CASE REPORT

A 27 years old male presented in September 2012 with unquantified weight loss, fever and night sweats of 02 months duration. On examination was found to have oral candidiasis and all other systemic examination was unremarkable. He was tested and confirmed to have HIV 1 infection with CD 4 count of 419 cells/ cumm. Chest X- Ray revealed non homogenous opacity in left upper lung zone with ESR 70mm at the end of first hour and Mantoux reading of 10mm at the end of 72 hours. There was no Acid Fast Bacilli (AFB) in the sputum. After trial of antibiotics for five days individual did not show any symptomatic improvement.

Hence based on clinical symptoms of weight loss, fever and night sweats, chest X-Ray findings, high ESR and significant reactive Mantoux reading in an individual of HIV infection Anti Tubercular Therapy (ATT) was started consisting of 2 HRZE + 4 HR for sputum negative pulmonary tuberculosis. Septran prophylaxis was started and it was decided to start HAART after completion of ATT as CD 4 count was 419 cells/ cumm and individual had WHO clinical stage 3 condition. He was also treated for oral candidiasis with fluconazole and oral clotrimazole mouth paint with marked improvement in signs and symptoms. After 06 months of ATT he improved clinically with resolution of the non homogenous opacity in the chest X-Ray.

He was started on HAART (AZT + 3TC + NVP) with lead in time of 14 days for NVP (200mg once daily) and thereafter the dose of NVP was escalated to 200mg twice daily with good tolerance and no adverse drug reaction. His CD 4 count at the start of HAART was 423 cells/ cumm.

One week after the escalated dose of NVP the individual developed sore throat, fever, malaise and moderate headache with

ocular complaints. Two days later generalized skin eruption with involvement of mucous membrane of genitalia, oral cavity and swollen eyelids in the form of crusted and ulcerated lesions with ensuing pain and photophobia developed. He had erosions on the lip and mouth with purulent conjunctivitis (Figure 1).

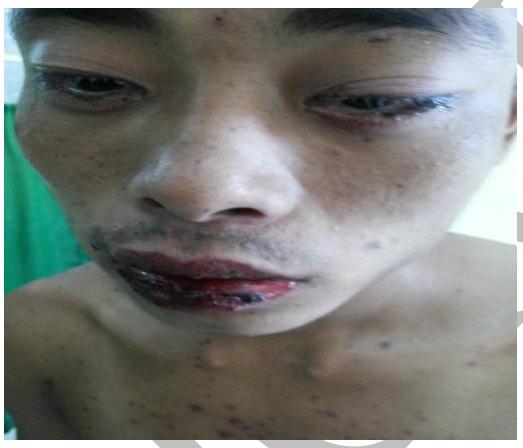

Figure 1: Erosions on lip and mouth with purulent conjunctivitis

The cutaneous lesions consisted of non confluent purpuric macules and positive Nikolski, i.e detachment of epidermis on pressure (Figure 2 & 3).

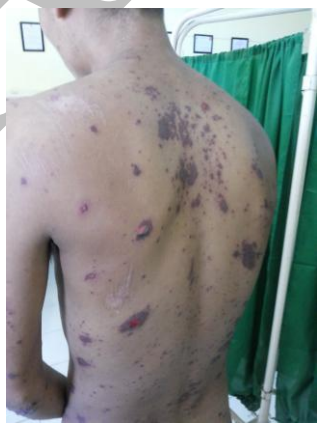

Figure 2: Positive Nikolski Sign's

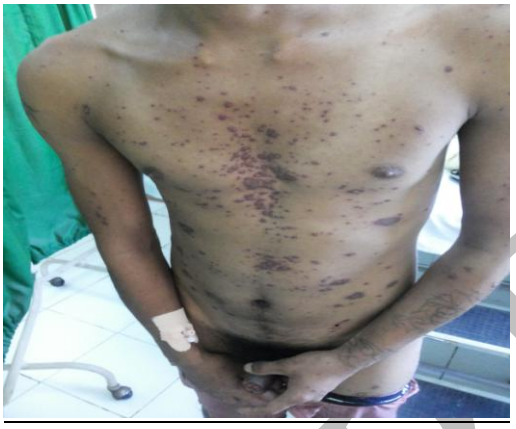

Figure 3: Non confluent purpuric lesions with urethra mucosal involvement

His hematological investigation revealed WBC count of 10X 10^9 / ltr with 62% neutrophils, 23% lymphocytes, 6% monocytes and 9% eosinophils. His ALT/ AST was 202 IU/ltr and 132 IU/ ltr respectively.

In view of severe skin eruption with mucous involvement and impaired hepatic enzymes after the escalating dose of NVP in HAART regimen all the anti retroviral drugs were withhold temporarily. The patient was treated with intravenous fluids oral steroids with gradual tapering, anta acids and H_2 receptor antagonist, regular anti septic dressing of skin lesions, ryles tube feeding, sterile ocular lubricants application, Antibiotic and steroid combination of eye drop, regular chlorhexidine mouth wash use and white soft paraffin application to the lips. Strict reverse isolation was maintained to prevent infection with change of peripheral lines twice a week was done. Removed tips and lines were sent for culture to decide on adding of IV antibiotics.

The patient condition improved in next 4 to 7 days (Fig 4& 5). The hepatic enzymes settled to normal values after 01 week and rechallenge with NVP was not done but he was started on Effaverenz as NNRTI along with NRTI's (AZT + 3 TC) after 3 weeks of complete resolution of signs and symptoms of adverse drug reaction. No recurrence of rash or derangement in Liver Funcyion Test was observed in subsequent follow up after 06 months but developed

symblepharon of both eyes which was managed with symblepharectomy.

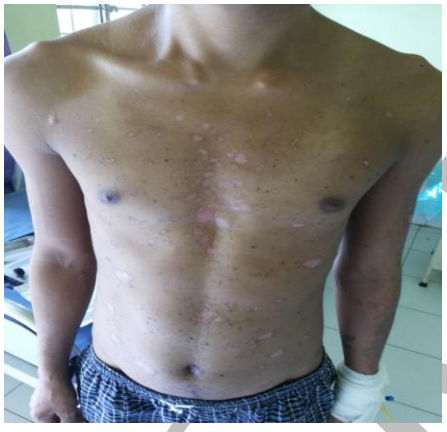

Figure 4: Post treatment lesions on front resolved

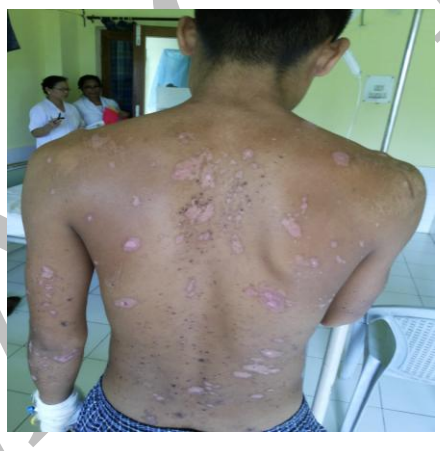

Figure 5: Post treatment lesions at back resolved

DISCUSSION

Anti retroviral therapy has increased the life expectancy of individual infected with HIV but we continue to encounter adverse drug reaction with individual component of HAART regimen. Typically drug reaction occurs within first six weeks of start of offending drugs[18, 19] and in our case also cutaneous manifestation started one week after the start of escalating dose of NVP (200mg twice daily) in the HAART regimen. The respect of a lead in period for

NVP does not appear to prevent SJS or TEN as seen in one of the study.[15] This was also observed in our case as despite lead in time of 14 days for NVP (200mg once daily) the individual developed SJS after 1 week of the start of NVP escalating dose (200mg twice daily).Reported risk factors for SJS include female sex, history of drug allergy, low body weight, high NVP plasma level and CD 4 count greater than 250 cells/ cumm in females and greater than 400 cells/ cumm in males.[19,20] In our case individual with CD 4 count 423 cells/ cumm was started on HAART regimen consisting of AZT + 3 TC + NVP after treatment with ATT for six months for sputum negative pulmonary tuberculosis, which is a WHO clinical stage 3 condition and is an indication to start HAART irrespective of CD 4 counts. SJS or TEN have been reported to occur in 0.3% of patients taking NVP within first 4 to 6 weeks of treatment.[19] Serious ocular complications may be seen in upto 100% of cases and may vary from chronic conjunctivitis to complete blindness. Symblepharon may form and it can immobilize the eye.[21, 22] In our case report we found that the individual developed symblepharon of eyes on follow up despite initial aggressive management of ocular lesions.

CONCLUSION

Individual infected with HIV 1 are at increased risk of developing severe mucocutaneous drug reaction including SJS and TEN. NVP based regimen of HAART have been widely used in resource restricted countries because of their efficacy, accessibility and comparatively low cost.[23]Currently exposure to NVP is the reason for persistence of high risk of SJS or TEN in relation to HIV infection.[15] NVP must be permanently discontinued in patients developing serious cutaneous reaction and alternative drug such as Effavirenz which has relatively lower risk of severe skin reaction can be started in HAART regimen. Early aggressive management is necessary in SJS which have high mortality in severe cases if left untreated. Serious ocular complications may be seen in upto 100% of cases despite initial aggressive management of ocular lesions.

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