Indian J Lepr 2012, 84 : 227-232

http://www.ijl.org.in

Case Report

Severe cutaneous adverse reactions due to isoniazid in a HIV Positive patient

BK Viswanath, P Ranka, M Ramanjanayalu

Received : 22.05.2011 Revised : 11.06.2012 Accepted : 13.06.2012

Severe Cutaneous Adverse Reaction (SCAR) represents the spectrum of adverse drug reactions from erythema multiforme, Stevens - Johnson syndrome (SJS) to Toxic Epidermal Necrolysis (TEN). A 55 year old lady presented in a toxic state with peeling of skin, blisters on the body of seven days duration following medications taken for fever and pulmonary tuberculosis. When referred to our institution, she was diagnosed as TEN. Immediately the suspected medications were stopped. The essential investigations were done including the screening for immunosuppression, which was found to be negative. The patient was treated symptomatically with emphasis on skilled nursing care. The patient's skin condition improved gradually but tuberculosis progressively worsened over three months. Thus patient was reinvestigated for seropositivity and was found to be positive! Considering the benefit - risk ratio along with the advice of the pulmonologist, a decision was made to give her a rechallenge test, first for antitubercular drugs and later for antipyretics. The patient developed SJS within two days of starting isoniazid (INH). On withdrawal of INH the patient recovered.

Key words : SCAR, Toxic Epidermal Necrolysis, Stevens - Johnson Syndrome, Isoniazid, HIV, Tuberculosis

Introduction

SCAR represents a spectrum of adverse reaction, from the lesser variant erythema multiforme to severe SJS-TEN respectively (Bilimoria and Shah 2008). TEN and SJS are acute life threatening conditions. Epidermal necrosis causes erosions of the mucous membranes, extensive detachment of the epidermis, and severe constitutional symptoms (Lyell A 1979). 3% to 8% of hospital admissions are due to SCAR, of which the incidence of TEN is 0.9 to 1.4 persons /million-year and SJS, at 1 to 6 case/million person-years (Bilimoria and Shah 2008, Breathnach and Hinter 1992, Roujeau et al 1995). It has been estimated patients with AIDS have a 1000-fold higher risk. SCAR is associated with a high risk of mortality and morbidity, requiring multidisciplinary treatment approach to prevent the same.

The reaction is idiosyncratic. The incubation period is typically a few days to three week, but less than 48 hours in a patient with a history of similar reaction to that drug (Revuz et al 1987,

[1] BK Viswanath, MD, Professor
[1] P Ranka, Resident (final year)
[1] M Ramanjanayalu, Resident (first year)
[1] Department of Dermatology and J J M Medical College
Correspondence to : BK Viswanath email : viswanath.bellulli@gmail.com

Guillaume et al 1987). Over 100 drugs have been implicated, the most common drugs are sulphonamides, antiepileptics, oxicam group of NSAIDS, antiretroviral drugs. SJS-TEN is also occasionally caused by viral infections (Kanwar et al 2004).

We are reporting this case due to the rarity of SCAR because of isoniazid alone. There are very few case reports reported in the literature (Kanwar et al 2004, Scheid et al 1999, Bomb et al 1976, Mittal et al 1976, Kvasnicka 1979).

Case Report

A 55 year old female patient (widow), was being treated for high grade fever and cough with expectoration in a nursing home. The patient was subjected to various investigations and was diagnosed to have pulmonary tuberculosis. The patient was subsequently started on anti-tubercular treatment (ATT) with 300mg INH, 450 mg rifampicin (R), 750 mg/day of pyrazinamide (Z) and 800mg of ethambutol (E) daily along with antipyretics. One week later patient developed few erythematous rashes on her legs which progressed to blisters within two days along with soreness of mouth and conjuctival irritation. The next day, the patient's relatives noticed peeling of skin in sheets involving almost 40 to 50% of the body surface area and erosions of buccal and vaginal mucosae respectively. The patient developed mucopurulent conjunctivitis. Immediately all the medications were dis-continued and the patient was referred to an higher institution.

At this stage, when first seen by us, patient was toxaemic. Her pulse was 130 beats per minute. The urinary output was less than 100ml during the last 24 hours. The skin was tender and Nikolsky's sign was found to be positive. Large areas on the trunk, lower limbs, forearms, face was covered with erythematous macules, few tense bullae and extensive peeling of the skin, haemorrhagic crusting was present on the lips (Figure 1). Tachycardia and low breath sounds was heard with stony dull percussion in the mammary,

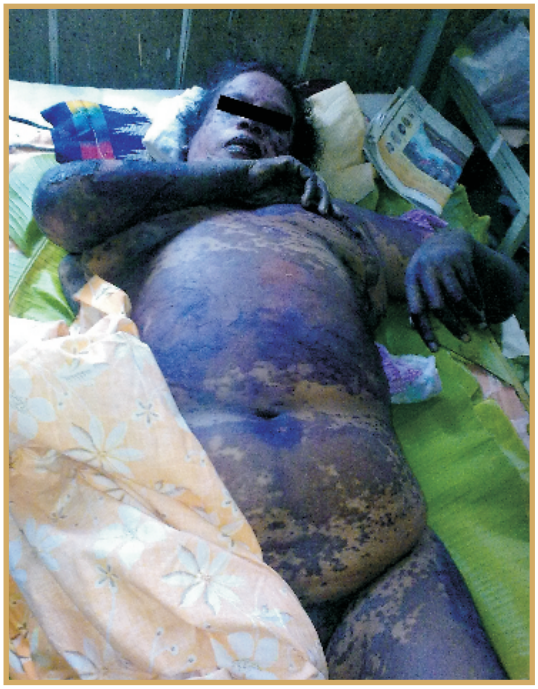

Fig 1 : Haemorragic crusting of lips with peeling of skin involving 40 percent of BSA.

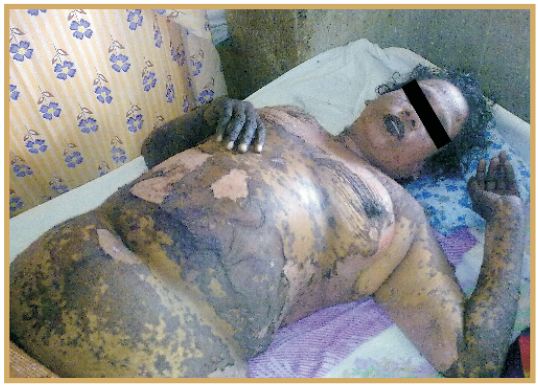

Fig 2 : Week after admission patient showing slight improvement.

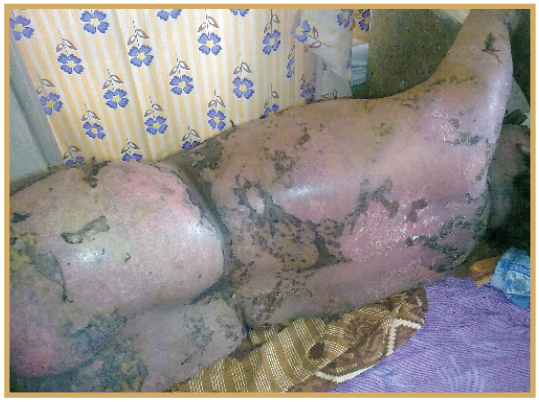

Fig 3 : Patient recovering well - one month following treatment.

infraaxillary and infrascapular areas and shifting dullness was positive. The other organ systems were within normal limits (Figure 2). All the essential investigations, including screening tests for immunosuppression was done and a diagnosis of TEN was made. SCORTEN was found to be 3.

The investigations revealed that the patient was anaemic with haemoglobin of 9g/dl and ESR 75 mm at the end of one hour. Chest X-ray showed features of pleural effusion and the pleural aspirate analysis confirmed it to be of tubercular etiology. Other biochemical parameters were within normal limits. The screening tests for seropositivity was found to be negative. Although in order to rule out the probability of technical error involving a clinical suspicion, a confirmatory test needed to be done. It could not be done due to lack of sophisticated laboratory facilities and financial constraints.

The Patient was shifted to an isolation ward and was treated symptomatically with special emphasis on skilled nursing care along with the restoration of fluid loss, temperature regulation, topical antibiotics for the erosions and azithromycin parentally to which good response was seen. Transfusion of two pints of cross

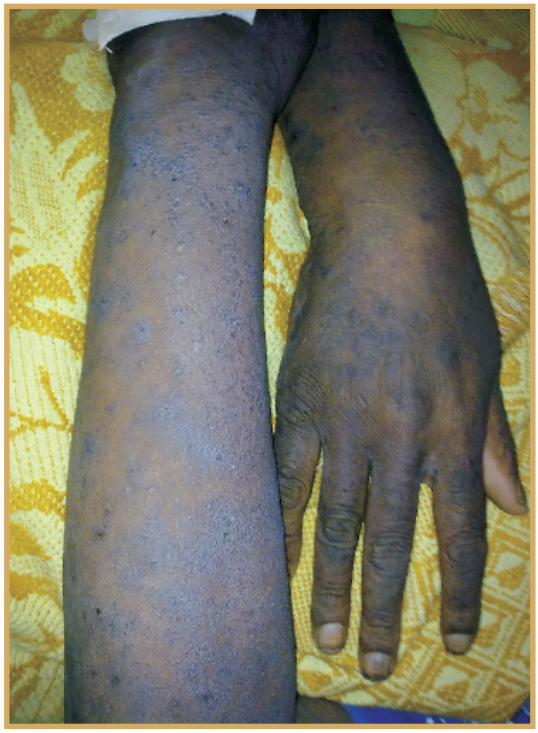

Fig 4 : Maculopapular rashes observed following the provocation with INH.

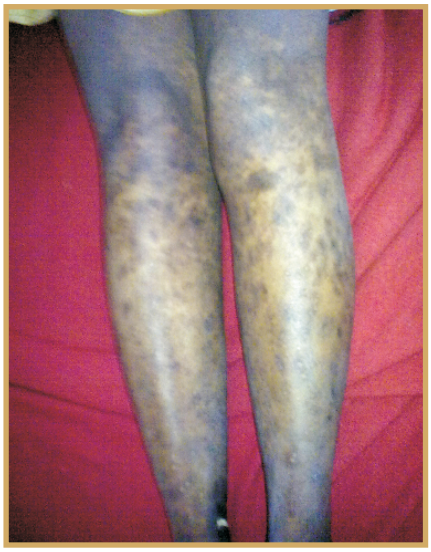

Fig 5 : Maculopapular rashes observed following the provocation with INH

matched blood aided in general well being and increased the ability to combat against all odds with the limited treatment options. The patient's condition improved gradually over three months (Figure 3). The general health of the patient was failing due to the tubercular status. On consultation with the pulmonologist a decision was made to reinvestigate her. The patient turned out to be HIV reactive with a CD_4 count of 64/µl. On examination for other OI, the patient tested negative. Thus it was decided after considering the benefit-risk ratio to give her a rechallange test to find out the causative drug and to restart treatment for the original tubercular infection. As the patient was taking ATT and paracetamol prior to the onset of TEN it was decided to go with ATT drugs first. There was no reaction to R in doses of 150mg and 450mg, given on the first two days. On the 3rd day after 50mg of INH she developed a mild reaction with few erythematous rashes but the reaction was unclear. Therefore next day she was given 100mg of INH, which led to a definite SJS reaction, with flat target lesions on the arms and generalized maculopapaular rash, few tense bullae on the lower back and legs, erosions of the buccal and labial mucosae respectively. Conjuctival chemosis was present (Figure 4 and 5), however, the reaction subsided on stopping INH. Subsequently, she was also tested with 200 mg and 800 mg of E, and with 250mg and one gram of Z without any adverse reactions. To complete the provocation test, she was administered paracetamol on the subsequent day, but there was no reaction.

Under supervision she was started on alternate drugs for tuberculosis and after the initial two weeks it had been decided to start on antiretroviral therapy. The patient's overall general condition improved and she is under regular follow up.

Discussion

Tuberculosis (TB) is the commonest opportunistic infection in a HIV positive patient in India. The risk of developing TB is estimated to be between 21-34 times greater in people living with HIV (PLHIV). According to the WHO - HIV-TB Facts 2011 : in 2010 13% (1.1 million / 8.8 million cases) of new TB cases being among PLHIV, 24% of all TB deaths being associated with HIV and 22% of HIV related deaths caused by TB. In India, 2.5 million are currently infected with HIV of whom 40% are co-infected with TB (Maniar et al 2006).

Patient with HIV infection exhibit a unique susceptibility to *M. tuberculosis*. The rate of progression of TB infection to active disease following initial exposure is greater than 40% in people infected with HIV, compared to approximately 5% in non reactive patient. Deficiency of cell mediated immunity is the common denominator for both HIV and TB. Both these diseases have a long latency and together form a lethal duo, particularly in developing countries as very rightly quoted “PARTNERS IN CRIME” by Maniar et al (2006).

The incidence of adverse drug reactions is 1000 fold higher in a HIV positive patient due to exposure to multiple drugs and also inherently greater risk of reaction due to decrease in systemic glutathione that decreases the capacity to scavange hydroxyl amines derivatives of sulphamethoxazoles reactive metabolities (Bilimoria and Shah 2008).

With the advent of the HIV pandemic in the developing countries, tuberculosis has continued to remain a challenge for healthcare professionals. HIV related TB shows a higher prevalence of extrapulmonary and disseminated TB and adverse events because of ATT treatment. However, following use of fixed drug regimens under NTCP programme, use of thiacetazone has declined tremendously during the last decade,

thus contributing to a shift in the spectrum of drugs causing TEN (Kanwar et al 2004).

As in developed nations, anticonvulsants are today the most commonest group of drugs that cause TEN in developing countries. HIV/AIDS patients are an important subgroup of patients who are particularly susceptible to SCAR. There is a constant increase in the number of antiretroviral and sulphonamide-induced TEN, SJS in HIV-infected patients (Kanwar et al 2004).

Adverse drug reactions are more common in HIV-infected individuals than in their normal counterparts. A high frequency of drug reactions (>20%) has been noted in HIV-infected patients on ATT. In a study 79.5% patients showed adverse events, most commonly gastritis (93.5%), followed by hepatitis (46.5%) and skin rashes (5.5%). Co-infection with HBV and HCV may play a role in the genesis of drug-induced hepatitis (Maniar et al 2006).

Incidence of adverse reactions to INH, estimated to be 5.4%, with most prominent reactions being cutaneous eruptions (2%), fever (1.2%), jaundice (0.5%) and peripheral neuritis (0.6%). Cutaneous side effects due to INH is only 2% of which acneiform eruptions is the most common and SJS-TEN is very rare. Hypersensitivity reactions produce urticarial, angioneurotic edema, and morbilliform eruptions, which may occasionally progress to exfoliative dermatitis. Other skin lesions noted include xerostomia, nonthrombocytopenic purpura, striae cutis atrophica, pruritus, erythema. LE and pellagra like syndromes found to be common in slow acetylators (Holdiness 1985).

As we know the progression to clinical disease is faster and more severe in HIV-positive patients. It is important not to switch the first line TB drugs (especially INH and R)without evidence of an association with a serious side effect. Use of sequential rechallenge provocation test to decide the causative drug and in case of severe allergic reactions the provocation tests should be performed cautiously and sequentially under supervision starting with one-tenth of the full dosage (Holdiness 1985).

As mentioned earlier very few case reports about SJS - TEN due to isoniazid alone has been documented, it is important to keep INH also as a possibility of SCAR, as quoted by Walter Shelley and E Shelley "*Anything you can think of, anything you can see, and some things you don't even think of can be due to a drug!*".

Acknowledgement

We would like to acknowledge staff and residents of Department of dermatology, JJMMC. We would also like to thank Dr Sarah, Dr Tina, Dr R Masthi and Mr Mahesh for their tremendous help in completion of this article.

References

1. Bilimoria FE and Shah JB (2008). Drug Reactions. In: IADVL Text Book Of Dermatology, 3rd edn, Vol II (Valia RG, Valia RA eds), Bhalani Publishing House, Mumbai, pp 1633-1668.
2. Bomb BS, Purohit SD and Bedi HK (1976). Stevens-Johnson syndrome caused by isoniazid. *Tubercle*. **57**: 229-230.
3. Breathnach SM and Hinter H (1992). Introduction and Incidence of Drug Reactions. In: Adverse drug reaction and the skin (Breathnach SM, Hinter H eds), Blackwell Scientific Publishing, London, pp3-13.
4. Guillaume JC, Roujeau JC, Revuz J et al (1987). The culprit drugs in 87 cases of Toxic Epidermal Necrolysis (Lyell Syndrome). *Arch Dermatol*. **123:** 1166-1170.
5. Holdiness RM (1985). Adverse Cutaneous Reactions to Antituberculosis Drugs. *Int J of Dermatol*. **24:** 280-285.
6. Kanwar AJ, Dogra S and Kumar B (2004). Changing Pattern of drug induced toxic epidermal necrolysis in developing countries. *Clin and Experimental Dermatol*. **29:** 423-436.

7. Kvasnicka J, Rezac J, Svejda J et al (1979). Disseminated Intravascular Coagulation associated with toxic epidermal necrolysis (Lyell's syndrome). *British J of Dermatol*. **100**: 551.
8. Lyell A (1979). Toxic epidermal necrolysis (the scalded skin syndrome):a reappraisal. *British J of Dermatol*. **100**: 69-86.
9. Maniar KJ, Kamath K, Mandalia Set al (2006). HIV and Tuberculosis: Partners in Crime. *Indian J Dermatol Venereol Leprol*. **72:** 276-282.
10. Mittal OP, Singh RP and Katiyar SK (1976). Toxic Epidermal Necrolysis due to isoniazide. *Ind J Tuberc*. **23:** 32-35.
11. Revuz J, Penso D, Roujeau JC et al (1987). Toxic Epidermal Necrolysis: Clinical findings and prognosis factors in 87 patients. *Arch Dermatol*. **123**: 1160-1165.
12. Roujeau JC, Kelly JP, Naldi L et al (1995). Medication Use and the of Stevens - Johnson Syndrome Or Toxic Epidermal Necrolysis. *N Engl J Med*. **333**: 1600-1607.
13. Scheid P, Kanny G, Tréchot PH et al (1999). Isoniazid-induced bullous skin reaction. *Allergy*. **54:** 287-296.
14. WHO (2011). Guidelines for intensified tuberculosis case finding and isoniazid preventive therapy for people living with HIV in resource-constrained setting.

How to cite this article : Viswanath BK, Ranka P and Ramanjanayalu M (2012). Severe cutaneous adverse reactions due to isoniazid in a HIV Positive patient. *Indian J Lepr.* **84** : 227-232.