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CASE REPORT

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Analysis of severity and preventability in patients of—Toxic epidermal necrolysis—A case series

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Abstract

SJS-TEN is life-threatening autoimmune disorder triggered due to drugs such as analgesics, antibiotics, anticonvulsants, and antipsychotics. This report provides awareness to the Clinicians regarding prescription of drugs which cause SJS-TEN. Among young females of 20-40 years, screening for previous history, issuing drug alert cards, and preventing OTC prescriptions decreases mortality.

KEYWORDS

adverse drug reaction (ADR), intensive care unit (ICU), over the counter (OTC), Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN)

1 | INTRODUCTION

Steven-Johnson syndrome with detachment >30% of body surface area is called toxic epidermal necrolysis. Four female patients (20-40 years) of TEN on analgesics, antibiotics, and anti-epileptic drugs (duration 3-13 days) were analyzed for severity and preventability. Early treatment, preventing OTC sale, screening HLA-B*1502 gene decrease mortality of TEN.

Steven-Johnson syndrome is a rare autoimmune disorder, which includes skin and mucous membrane. Characterized by fever, blistering, erythema, maculopapular lesions, and mucosal involvement with more severe form being toxic epidermal necrolysis syndrome or Lyell's syndrome.[1,2] Factors include HIV infection, weak immune system, history of SJS drug use, family history of SJS, and genetic variations of HLA-B*1502, triggered by infection such as pneumonia or drugs. Drugs which cause SJS include anticonvulsants and antipsychotics, antibacterial sulfonamides, septran, analgesics such as paracetamol, naproxen, ibuprofen, antigout medication like allopurinol, and antiretroviral medication such as Nevirapine. It occurs during usage of drugs or 2 weeks of discontinuation of drugs. Complications include dehydration, sepsis, ophthalmic inflammation, acute respiratory failure, and permanent skin damage. Among various adverse drug reactions, cutaneous ADR Steven-Johnsons syndrome is <10% of body surface area involvement, SJS overlapping with TEN is 10%-30% involvement and Toxic epidermal necrolysis >30%, and it is fatal and life-threatening.[3] Emphasis of this case series is to analyze seriousness and severity of life-threatening ADR SJS-TEN, management and outcomes, and preventability to implement preventive measures such as genetic screening for gene variations in HLA-B*1502 before using above-mentioned drugs, prevent using medication if past history of SJS is seen, issuing drug alert cards and screening close relatives for genetic risk factors and avoiding use of drugs. Causality assessment of ADRs was performed by WHO-UMC scale,[4,5] severity

assessed by Hartwig and Siegel Scale, and preventability assessment by Schumock and Thornton scale.[13-15]

2 | CASE DESCRIPTION

2.1 | Case 1

A 21-year-old female patient presented with chief complaint of erythematous lesions all over the body with severe pain to Santhiram General Hospital, Nandyal. Patient was administered one dose of Capsule Amoxycillin 500 mg, Tablet Nimesulide 100 mg, and Tablet Aceclofenac + Paracetamol 100 + 500 mg for toothache from a local practitioner for which she developed fever and erythematous bullous vesicular lesions on upper limb followed by trunk lower limbs and scalp, erythema of conjunctiva with acute conjunctivitis, and watering of eyes with hemorrhagic ulcerations of buccal mucosa, lips, and genitals within 1 day of drug administration. Patient was diagnosed Steven-Johnson syndrome with toxic epidermal necrolysis (>30% body involved) admitted in intensive care unit and treated accordingly. Ophthalmic examination showed acute conjunctivitis and watering of eyes. Patient was conscious on examination, and vitals were stabilized after admission. Offending drugs were withdrawn treated with IV Injection Hydrocortisone 100 mg BD, Tab Ceftas 200 mg BD, Tab Atarax 10 mg OD, Diprovate cream twice for application, Tab Paracetamol 500 mg SOS, injection Rantac 50 mg BD, Injection Potassium Chloride, and IV fluids. Patient recovered in 6 weeks and was discharged, suggestive of positive temporal relation between drug and event with positive dechallenge wherein reaction subsided once drug was abated and rechallenge was not done. It is a serious, probable, severe (Grade VI), preventable type of reaction wherein patient recovered after 6 weeks of treatment and was discharged.[6,7] (Figure 1).

2.2 | Case 2

A 35-year-old female patient was admitted to ICU, Bhaskara General Hospital, Hyderabad, with chief complaints of extensive rash and fluid filled vesicles on skin of face, neck, and all over the body. Erythema of conjunctiva, ulceration of lips, and oral cavity was associated with severe pain. Past history of patient reveals that she underwent surgery for open reduction of Grade III distal radius and ulnar fracture and was treated with Tab Cifran 500 mg and Tab Septran 400 + 80 mg OD. After 8 days of administration, patient developed fever, vomiting, itching, rash, loose stools, and was admitted in ICU. On examination, patient was unconscious had fever, erythematous nonblanchable, generalized, bullous maculopapular eruptions on neck, face, trunk, and upper limbs with lesions of varied sizes, oral examination revealed ulcerations of lips, mucosa, tongue, and palate which are hemorrhagic and tender on palpation. Ophthalmic examination revealed subconjunctival hemorrhagic lesion with pus discharge. Vitals such as pulse rate: 110/min and BP: 90/50 mm Hg were recorded. Investigations revealed Hb: 8.4 g/dL, RBC: 3.7 cu mm, WBC: 19 800 cu mm, and ESR: 32 mm/1st hr In spite of development of reaction on 8th day, both drugs were administered for another 5 days, and total administration was for 13 days. Histo-pathological examination report of skin biopsy revealed Steven-Johnson syndrome. Nikolsky's sign was positive, and patient was treated with injection Hydrocortisone 100 mg IV 8th hourly, injection Avil IM 1 mL, injection Adrenaline 0.5 mL IM, followed by oral steroids, Tab. Prednisolone 10 mg QID, TID, BD, OD for 5 days, Tab Cefaclor 200 mg BD, Gentian violet, 1% Clotrimazole cream for application, and 0.3% Ofloxacin eye drops BD. Lesions healed after 6 weeks, and patient recovered. It is a serious, probable severe level VI, preventable type of reaction. Patient recovered with hyperpigmented skin and was discharged.[8,9] (Figure 2).

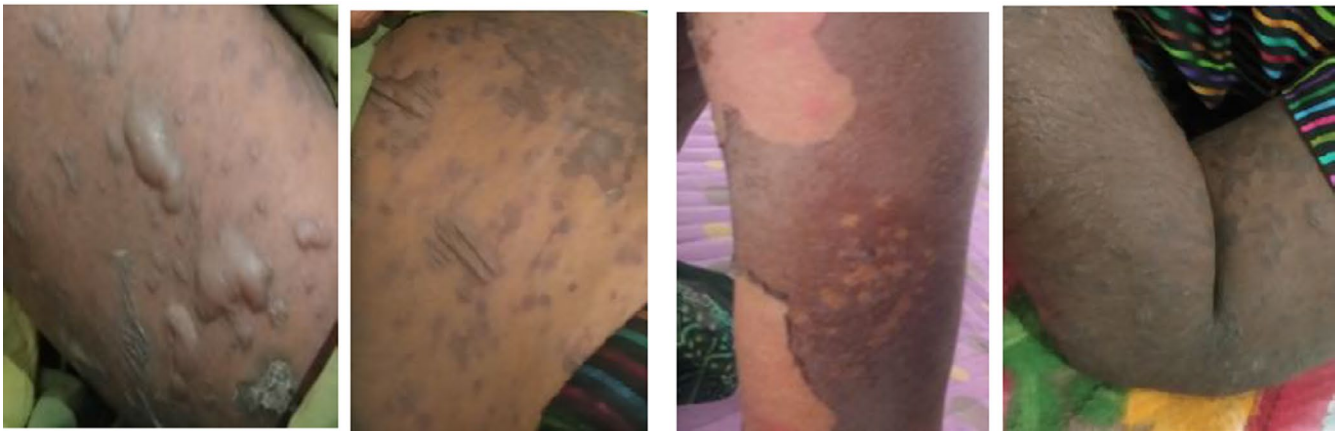

FIGURE 1 A 21-y-old female patient presented with erythematous lesions all over the body with severe pain

2.3 | Case 3

A 33-year-old female patient admitted in ICU, Bhaskara General Hospital with chief complaints of fever, macular, and bullous vesicular lesions all over the body. Lesions were erythematous, ulcerative, hemorrhagic, and seen over lips and oral mucosa. Past history reveals patient presented with seizure episodes for which tab Phenytoin 100 mg BD was administered for which she developed Steven-Johnson syndrome on 13th day of drug administration. Vitals were stable, PR: 100/min, BP: 130/80 mm Hg, CBP was normal and raised, and ESR values were seen. Skin biopsy confirmed Steven-Johnson syndrome. Ophthalmic examination revealed conjunctivitis with watering of eyes. Patient treated with injection Hydrocortisone 100 mg, IV 8th hourly, Injection Avil 1 mL OD, IV fluids NS, DNS, Tab. Augmentin 625 mg BD, 1% Clotrimazole cream with saline packs for wound dressings and patient recovered after 6 weeks with healed lesions with hyperpigmented macules. Positive temporal relation between drug and event is seen as reaction developed after 13 days of administration of Phenytoin and reaction subsided after the drug was withdrawn. Rechallenge is unknown. Hence, it is serious, severe (level VI), probable, and preventable type of reaction. Patient recovered and discharged after 6 weeks.[10] (Figure 3).

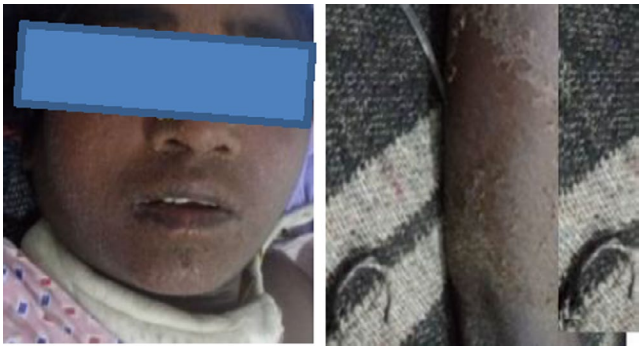

FIGURE 2 A 35-y-old female patient with extensive rash and fluid filled vesicles on skin of face, neck, and all over the body

2.4 | Case 4

A 8-year-old female child was admitted in ICU, Apollo Hospital, Hyderabad, with complaints of erythematous maculopapular rash all over the body. Past history reveals patient presented with seizure episode and was administered Tab. Lamotrigine 25 mg BD, after which patient developed erythematous maculopapular rash all over the body with ulcerations of lips and buccal mucosa. Vitals were stable, and on investigations, no other organs were involved. Skin biopsy revealed Steven-Johnson syndrome, due to anti-epileptic drug Tab. Lamotrigine. Patient was treated with IV steroids, IV fluids, antibiotics, antifungals, and saline dressings. Patient recovered after 4 weeks. This suggests positive temporal relation between drug and event with positive dechallenge, and it is serious, severe (level VI), probable, preventable type of reaction. Patient recovered and discharged after 4 weeks.

SJS-TEN is described as epidermal detachment of >30% of body surface area. In our case series, all patients are females with age group between 20-40 years in correlation with study done by Abarna Devi et al. 24% analgesics, 44% antimicrobials, 18% anti-epileptics, cause SJS-TEN. Duration of reaction is in between period 3 days to 13 days with correlation to Abarna Devi et al, study which is 6 days.[1,2] Signs and symptoms were seen after 1-3 days with fever, lesions involvement of mucous membranes with epidermal detachment with 3-5 days, leading to dehydration, severe pain to bleeding, hypothermia, and infection. No organ involvement such as liver, kidney, esophagus, strictures in small bowel and colon, disseminated intravascular coagulation seen, and ophthalmic complications treated without vision loss. All patients recovered in 4 weeks to 6 weeks. Intravenous corticosteroids, fluid balance, and aseptic care of wounds form the main stay of treatment. All patients recovered without sequel except hyperpigmentation of skin. Further studies are needed to delineate cause with more number of patients. A similar review of case incidence was reported by Sudip Das et.al, where incidence of skin reaction to Lamotrigine in children is 1:100 compared to adult is 1:1000.[11,12] Causality assessment of ADRs was performed by WHO-UMC scale, severity assessed by Hartwig

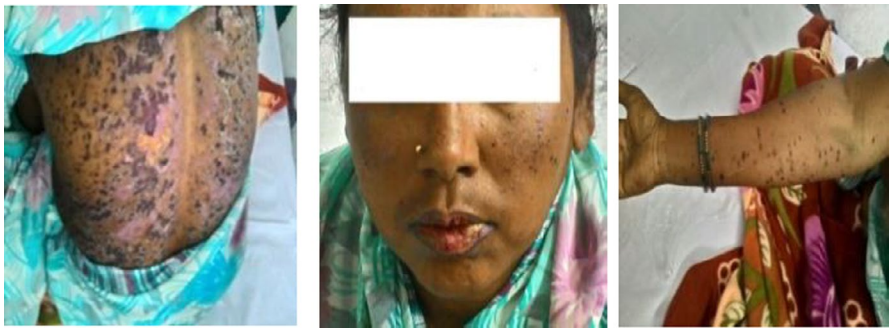

FIGURE 3 A 33-y-old female patient with erythematous, ulcerative, and hemorrhagic lesions seen over lips and oral mucosa

and Siegel Scale, preventability assessment by Schumock and Thornton scale.[13-15] Admission of patients into ICU for treatment suggests Level VI severe reaction according to Hartwig and Siegel scale, and careful titration of drug levels and gene screening suggests it preventable type of ADR according to Schumock and Thornton scale.

3 | FUTURE PERSPECTIVE

Antimicrobials, NSAID's, and anti-epileptics are the most common offending drugs for SJS-TEN, and hence according to our case series, female patients with age groups 20-40 years should be screened before administration of drugs. Patients with previous history of drug allergy and patients with history of genetic variations of HLA-B*1502 should strictly avoid use of medication. Strict regulations are needed for withdrawal of offending agent, stopping OTC sale, management at multispecialty ICU center, provision of facility for genetic screening at hospitals, and increase in awareness among healthcare professionals and patients about drug factors of SJS-TEN reduce morbidity and mortality. Approach toward personalized medicine, tailoring down treatment to individual genetic variations, and adequate epidemiological survey are the supportive measures. These measures reduce hospital duration stay and cost burden on patients. Further studies are needed to delineate HLA-B*1502 gene and provision needed for genetic screening in hospitals especially in developing and resource limited countries. Awareness of causative factors can avoid severe and preventable type of reactions.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

Dr Deepa Latha Ciddhavaduta, Professor & Head, Department of Pharmacology, Santhiram Medical College, Nandyal. cdeepalatha@gmail.com was a coordinator of ADR Monitoring Center, main visionary of case report, conception of design, acquisition of data, analysis, and interpretation. Dr V. Kalaiselvan, Principal Scientific Officer, Indian Pharmacopoeia Commission, Ghaziabad. vivekarts@gmail.com. National Coordination Center collect, collate, and analyze ADRs data and recommend regulatory interventions to Central Drug Standard Control Organization and prepared manuscript. Dr M. Madhavi Latha: Professor, Department of Dermatology, Santhiram Medical College, Nandyal. vc.madhavi@gmail.com. involved in treating Consultant Dermatologist for ADR patients and reviewed the manuscript. Dr Baloju Deepika: ADR Monitoring Center, Bhaskar Medical College, Moinabad. balojudeepika@gmail.com involved in patient safety vigilance technical associate of AMC involved in collection of cases and updates into Vigiflow, from various hospitals. Scientific Research Committee and Institutional Ethics Committee clearance is obtained.

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