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## Case Report

# A rare case report of diclofenac induced Steven Johnson syndrome

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### ABSTRACT

Stevens Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are acute life-threatening mucocutaneous diseases characterized by extensive necrosis involving the mucous membrane and epidermis. In this case, a 54-year-old female after intake of prescribed diclofenac tablet presented with multiple reddish maculopapular eruptions over face, abdomen, both limbs, over lips and oral cavity associated with pain and intense pruritus. This case is a rare presentation of drug induced SJS caused by commonly prescribed NSAID, diclofenac. Patient's condition improved after withdrawal of offending drug and prompt treatment. This case suggests that emphasis on early detection, assessment and timely management of adverse drug reactions is of utmost importance. Thus, establishment of proper vigilance centre and regular monitoring is necessary and taking caution in prescribing drugs as well in elderly groups.

**Keywords:** Steven-Johnson syndrome, Diclofenac, Adverse drug reaction, Pharmacovigilance

### INTRODUCTION

Stevens Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) are acute life-threatening mucocutaneous diseases characterized by extensive necrosis, mucous membrane involvement and detachment of epidermis, differing only in their degree of severity.<sup>1</sup> The incidence of SJS and TEN is estimated to be 1-6 and 0.4-1.2 cases per million person-years respectively.<sup>2</sup> The first case of SJS was described in 1922 as an acute mucocutaneous syndrome in two young boys.<sup>3</sup> SJS and TEN are classified according to body surface area (BSA) involvement. SJS is characterized by <10% detachment of the BSA with wide-spread erythematous or purpuric macules or flat targets, overlapping SJS and TEN was considered to be 10-30% detachment of BSA and TEN with >30% detachment of BSA.<sup>4</sup> Drugs are found to be one of the important causes and more than 100 drugs have been implicated in causing SJS and TEN.<sup>3</sup> Other etiological factors are idiopathic, infections and malignancy. The high-risk groups of drugs in SJS include antibacterial sulfonamides, aromatic anticonvulsants, allopurinol, oxycam nonsteroidal anti-inflammatory drugs (NSAID),

lamotrigine and nevirapine. Many NSAIDs were suspected to be associated with SJS and TEN.<sup>1</sup> SJS can occur at any age group however; the risk increases with age after the fourth decade and more frequently affect elderly women.<sup>1</sup> HIV-AIDS patients, immunodeficiency patients, family history of the condition and variation of gene called HLA-B are at higher risk of developing SJS.<sup>3-5</sup> The specific gene marker HLA-B 1511 has been identified as risk factor for carbamazepine induced SJS in Japanese patients.<sup>6</sup>

Nonsteroidal anti-inflammatory drugs (NSAIDs) are group of drugs that has been used in various conditions to decrease pain and inflammation by inhibiting both the isoforms of cyclooxygenase enzymes (COX-1 and COX-2) of which cyclooxygenase-1 is responsible for the adverse effects and cyclooxygenase-2 for the therapeutic effects.<sup>7</sup> Diclofenac is one of the most frequently and extensively used NSAID as analgesic and anti-inflammatory agent. The most common adverse drug reactions of diclofenac include impairment in gastrointestinal, hepatic and renal functions whereas the skin reactions are very rare. Thus, we present a rare case

report of diclofenac induced Steven-Johnson syndrome (SJS) in an elderly woman that was identified and reported to the ADR reporting centre of our medical college. Prior consent was taken from the patient before observing the case and subsequent follow ups were done during hospitalization period in Dermatology department of Jorhat Medical College and Hospital.

### CASE REPORT

A 54 years old female patient reported to the Outpatient Department (OPD) of Dermatology department of our hospital with complaints of multiple reddish maculopapular eruptions over face, abdomen, both limbs, over lips and oral cavity with difficulty in swallowing. It was associated with pain and intense pruritus which was sudden in onset. The patient was well built and well-oriented and on examination; blood pressure was 130/70 mmHg, pulse rate was 74 beats per minute (bpm), appetite was decreased. On cutaneous examination, there were multiple dusky red atypical target lesions over forearms, both upper and lower limbs as well as over abdomen with excoriation marks (Figure 1 and 2). Intraoral examination revealed ulcerations and odema of the vermilion border of lips, raw areas over buccal mucosa as well as on surface of the tongue and palate (Figure 3 and 4). The lesions covered <10% of the body surface area (BSA). Genital mucosa was not affected.



**Figure 1: Target type lesion over lower limb.**



**Figure 2: Atypical target type lesions over upper limb with excoriation marks.**



**Figure 3: Raw areas over buccal mucosa.**



**Figure 4: Ulceration and odema of lips.**



**Figure 5: Healed ulcer over lips after treatment.**



**Figure 6: Healed areas over oral cavity after suspending offending drug.**



**Figure 7: Healed lesion over arm and forearm.**

On taking past medication history, we found that she had pain over left shoulder joint for which she was prescribed tablet diclofenac 75 mg twice daily for 5 days by a general practitioner. She had taken single dose of diclofenac 75mg tablet at night after food. On the next day she started experiencing intense itching and multiple lesions over skin. Medication history also revealed that she had been taking levothyroxine 25 µg tablet once daily for past few years (concomitant medication). From all the signs and symptoms, the dermatologist made a diagnosis of Steven-Johnson syndrome (SJS).

Investigations of the patient revealed high neutrophil count (77.4%), raised serum urea (39 mg/dl), serum creatinine (1.6 mg/dl) and C-reactive protein (70.26 mg/l). Routine

examination of urine, random blood sugar level, thyroid profile (T3=0.85, T4=9.62, TSH=1.32) and liver function tests were within normal limit.

The suspected offending drug, diclofenac, was withdrawn immediately on identification. Prompt treatment started with systemic steroid injection dexamethasone, antimicrobial injection linezolid 600 mg twice daily, and infusion DNS 500 ml once daily. Supportive measures for mucosal erosion Condy's compress and gargle were given. Pain over shoulder was managed with tramadol 100 mg tablet. Later, the patient was prescribed tablet fluconazole 100 mg twice weekly and fucidic acid cream. Carboxymethylcellulose eye drops were given to prevent ocular complications. The severity of illness and prognosis of the patient was assessed using the SCORTEN severity-of-illness Score 3. In our present case the total SCORTEN score of the patient was 2 (Table 1). The patient was closely monitored during the treatment course and improvement was noticed after initiation of treatment (Figure 5, 6 and 7).

On causality assessment using the Naranjo causality assessment scale, diclofenac was found to have probable causal relationship with emergence of SJS in this case. Re-challenge was not done in our case. The ADR was reported to the ADR Monitoring Centre of our hospital and the case was sent to National Co-ordination Centre (NCC) of Pharmacovigilance programme of India (PvPI) at Indian Pharmacopoeia Commission (IPC) through vigi-flow portal with worldwide unique no. IN-IPC-300642464.

**Table 1: SCORTEN severity-of-illness score of the case.**

| Prognostic factors                                    | Individual score | SCORTEN (sum of individual scores) | Predicted mortality (%) | Score in our case |
|-------------------------------------------------------|------------------|------------------------------------|-------------------------|-------------------|
| Age>40 years                                          | Yes=1, No=0      | 0-1                                | 3.2                     | 1                 |
| Malignancy                                            | Yes=1, No=0      | 2                                  | 12.1                    | 0                 |
| Tachycardia (>120 bpm)                                | Yes=1, No=0      | 3                                  | 35.8                    | 0                 |
| Initial body surface area detachment >10% involvement | Yes=1, No=0      | 4                                  | 58.3                    | 0                 |
| Serum urea >28 mg/dl                                  | Yes=1, No=0      | >5                                 | >90                     | 1                 |
| Serum glucose > 252 mg/l                              | Yes=1, No=0      |                                    |                         | 0                 |
| Serum bicarbonate <20 mmol/l                          | Yes=1, No=0      |                                    |                         | 0                 |
| <b>Total score</b>                                    |                  |                                    |                         | <b>2</b>          |

## DISCUSSION

Adverse drug reactions (ADRs) remain a major health issue in therapeutics worldwide. ADRs may affect the treatment outcomes; increase the rate of hospital admissions, increase morbidity and mortality, increase the cost of therapy, adversely affect the quality of life and overall patient satisfaction to health care.<sup>8</sup> SJS is a severe skin reaction most often triggered particularly by

medications. Patel et al reported the major causative drugs of SJS include antimicrobials (37.27%), anti-epileptic drugs (35.73%) and NSAIDs (15.93%). Carbamazepine (18.25%) and Phenytoin (13.37%) accounts maximum among the anti-epileptic drugs, whereas fluroquinolones (8.48%) have the maximum potential among the antimicrobials. Among NSAIDs, paracetamol (6.17 %), nimesulide (2.83%), diclofenac (2.06%) and piroxicam (0.26%) causes SJS. Other drugs causing SJS includes

isoniazid, amoxicillin, nevirapine, cotrimazole, sulphonamides, cephalosporins, pyrimethamine and sulfadoxine etc.<sup>9</sup> Chung et al discovered that there is a unique and strong association in Han Chinese between HLA-B 1502, SJS and carbamazepine.<sup>10</sup> Other etiological factors include HIV, hepatitis virus, herpes virus, mycoplasma pneumonia.<sup>11</sup>

The initial symptoms of SJS/TEN can be unspecific and may include fever, sore throat stinging eyes and discomfort upon swallowing followed by cutaneous manifestations. Involvement of the buccal, genital and ocular mucosa occurs in most patients characterized by reddish or purplish rash which begins as blister and later peel to 'raw' areas of skin that are painful, evolving into large area of epidermal detachment.<sup>3,12</sup> There may be involvement of face, upper trunk, limbs and the rash may rapidly extend to different parts of the body within few hours to days.<sup>1</sup>

Differential diagnoses of SJS/TEN include pemphigus vulgaris, bullous pemphigoid, linear IgA dermatosis, paraneoplastic pemphigus, acute generalized exanthematous pustulosis (AGEP), disseminated fixed bullous drug eruption, staphylococcal scalded skin syndrome (SSSS). Direct immune fluorescence staining should be performed additionally, to rule out autoimmune blistering diseases.<sup>3</sup> There has been increase in the use of NSAIDs over the years that had led to increase incidence of hospitalization due to its adverse effects. Preventable NSAID-related hospital admissions have been reported to range from 7%-11%.<sup>13</sup>

Diclofenac act by inhibiting prostaglandin (PG) synthesis and is preferential cyclo-oxygenase-2 (COX-2) pathway inhibitors and is considered safer.<sup>14</sup> Study by Alpa Pragnesh Gor et al reported that out of 26 ADRs due to use of NSAIDs, 19 patients had ADR due to diclofenac, 4 were due to nimesulide and 2 were due to paracetamol. Out of those 19 patients, 14 had GIT related symptoms i.e., nausea, abdominal distress, gastritis, vomiting, etc and 3 patients had skin-related symptoms like urticaria and redness of skin which were mild in nature.<sup>7</sup>

Diclofenac is known to cause common adverse effects such as gastritis, peptic ulceration, and renal impairment while skin rashes are rare adverse effect.<sup>15</sup> There are few cases on diclofenac-induced SJS that has been reported so far. Babamahamoodi F et al reported a 65-year-old female patient that developed SJS after use of diclofenac suppository 100 mg twice a day for joint pain.<sup>16</sup> Another case reported by Wiwanitkit V et al about skin rash after intake of diclofenac tablet for arm pain.<sup>15</sup> Our case report also involves a 54-year-old woman taking diclofenac for pain over left shoulder joint.

Thus, it was noticed that diclofenac induced SJS mostly involve elderly age group. While another case reported by Suenaga H et al about a 35 year old male patient developed SJS due to diclofenac during treatment for splenic injury and mandibular fracture.<sup>17</sup> Moitra S et al also presented a

SJS case of a 62 year old female patient after taking diclofenac and serratiopeptidase combination for pain over heel.<sup>18</sup> Shetty et al reported a 45 year old female patient that developed SJS after taking diclofenac sodium for dental operation; and Bendi SR et al presented 65 year old women that developed SJS due to injection diclofenac sodium.<sup>12</sup> Thus, it was observed that the risk of developing adverse reactions because of diclofenac is commonly seen among female than male. Nevertheless, further studies are necessary in this field to understand the demographic pattern of patients having SJS after administration of diclofenac.

The management of SJS is multifaceted and begins with identification and cessation of the causative agent.<sup>20</sup> In our case, the causative agent that resulted in SJS is from the use of diclofenac as the patients started to improve after withdrawal of the suspected offending drug. Supportive care and adjunctive therapies such as corticosteroids, fluid, electrolyte management, nutrition management, infection control and proper wound care remains the mainstay of treatment.<sup>20</sup> In our case also, we have seen that systemic steroids, antibiotic therapy and fluid therapy were given to improve the patient's condition and prevent secondary infections. Complications and sequelae of SJS may include hyper and hypopigmentation of skin (62.5%), dystrophies of nail (37.5%) and ocular complications.<sup>21</sup> Prognosis in patients with SJS is evaluated with validated SCORTEN disease severity scoring system and a SCORTEN score of 3 or above should be managed in an intensive care unit if possible. The average reported mortality rate of SJS is 1-5%.<sup>3</sup> The SCORTEN disease severity score of our patient was 2 and was managed in the indoor department of dermatology.

Patient's medication history helps to identify any previous ADRs and thus preclude re-exposure to the drug.<sup>22</sup> Although the steps taken to manage an ADR vary from physician to physician, altering a dosage regimen or withdrawing a medicine suspected of causing an ADR are common methods of managing ADR in practice.<sup>22</sup> Although, diclofenac causes fewer incidence of skin related ADRs, reporting this rare case of SJS will provide feedback to the prescribers as well as make them aware about the flagged drugs which will further encourage ADR reporting and might improve patient's safety and care.

## CONCLUSION

SJS is a rare life-threatening adverse skin condition majority of which is caused by drugs. Diclofenac is a widely and extensively used NSAIDs having potential to cause varied adverse reactions including risk of skin reactions like SJS especially in elderly age group. Hence, the health care professionals should be aware of such condition while prescribing the drug especially in elderly group. A detailed medication history and past allergy history should also be considered very important. Early identification of an adverse drug reaction helps the physician to manage the patient and prevent further

complications of the condition. Strengthening the pharmacovigilance, clinical vigilance as well as reporting system may prevent future life threatening ADRs of drugs.

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