Theophylline and meloxicam-induced Stevens-Johnson syndrome (SJS): rare case reports

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Stevens-Johnson syndrome (SJS) is an infrequent, multisystemic, fatal, immune-mediated hypersensitivity reaction. SJS may be due to adverse effects of drug intake often characterized by mucocutaneous rash, bullae, and blisters spread over the skin and mucous membranes, hyperpigmentation, puffiness, erosive lesions on lips and face. The most common cause of drug-induced SJS is antimicrobials, followed by NSAIDs, allopurinol, antipsychotics, and antiepileptic drugs. Two cases of atypical SJS presentation associated with the use of theophylline and meloxicam are reported here. Early identification and appropriate corticosteroid therapy might improve the condition. The reason for publishing these case reports is to raise an alarm among our health care fraternity and common man regarding medication-induced SJS, which may be dreadful especially due to theophylline used in bronchial asthma and meloxicam used for osteoarthritis and thereby preventing the expected serious sequelae in SJS.

Keywords:
bronchial asthma, corticosteroids, meloxicam, osteoarthritis, Stevens-Johnson syndrome, theophylline

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Introduction

Among so many cutaneous adverse drug reactions (ADR), the classical pattern observed is the cytotoxic T-cell-driven drug reaction, exhibiting a higher genetic susceptibility in those with a particular type I major histocompatibility complex alleles by the individuals. An extensive array of clinical and histopathological manifestations with differing severity is often seen. Maculopapular rash is the most common feature in cutaneous ADRs, while the most grievous forms are the autoimmune Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS is also known as the Lyell syndrome, is a rare fatal mucocutaneous condition where there is detachment of the skin and mucous membrane for which multidisciplinary approach is needed [1]. General characteristics include rash, bullae and blisters on the skin, mucous membranes, hyperpigmentation, and painful swollen lesions on the lips and face that are erosive. SJS may be due to drug hypersensitivity (54–94% of cases) and the most common drug offenders are phenobarbital, phenytoin, carbamazepine, allopurinol, NSAIDs, erythromycin, cefotaxime, cotrimoxazole, and amoxicillin, which are generally considered to be safe. Next in 6–30% of cases, infections like mycoplasma pneumonia, rickettsia, mycobacterium,

cytomegalovirus, parvovirus, influenza virus, and 6–17% of cases are idiopathic [2]. People with genetic alleles at human leukocyte antigen (HLA)-B 5801 and HLA-B 1502 are predisposed to develop SJS/TEN. There is one published article on theophylline-induced SJS reported worldwide (reported in 1989 by Uzi Brook *et al.* in *Paediatr Dermatol* Vol. 6, No. 2, 126–129). This case report would be the first of its kind to point out the association of SJS and theophylline/meloxicam drug therapy in India [3].

Case report 1

A 32-year-old male patient came to the dermatology outpatient department with erythematous lesion all over the body for the past 3 months and swelling of lower limbs for the past 1 month. On examination, purpuric lesions (0.2×0.2 cm) over the trunk, back, and limbs, and annular scaly lesions (5×5–15×10 cm) in both upper limbs with scaling and fissuring on the palms were present. Curdy, creamy, cheesy precipitates were identified on the tongue and buccal mucosa. The face was covered with scaling and maculopapular lesions. The medical history revealed that 10 weeks before, the patient had an acute asthma attack and was treated by an rural medical practitioner with tablet theophylline 400 mg once daily, which he had never taken before. The patient continued to take the same tablet for the next 3 months and developed scaly lesions all over the body. The dermatologist diagnosed this as a case of SJS and he was treated with corticosteroids, ceftriaxone, systemic antifungals, and antihistamines. Lesions resolved in 25 days after which the patient was discharged successfully with a precautionary advice not to take theophylline in the future. This ADR is reported to be probable as dechallenge and temporal relationship is identified between the drug and the clinical manifestation of SJS (Fig. 1).

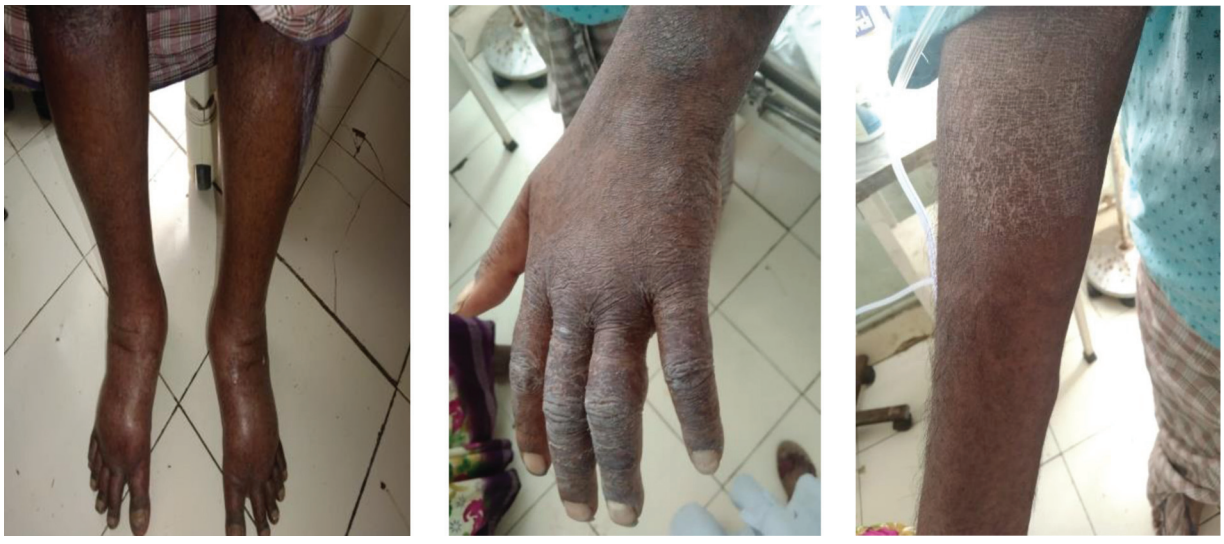
Case report 2

A female patient aged 39 years, came to the department of dermatology with maculopapular rashes over the lips, cheeks, and upper extremities developed in the last 3 days. The orthopedic doctor had prescribed her tablet Meloxicam for osteoarthritis 7.5 mg per day initially, later 15 mg per day for 1 month. At the end of 1 month, this untoward event occurred and the offending drug was immediately stopped by the dermatologist on diagnosing this case as Meloxicam-induced SJS. On hospital admission, the treatment initiated was intravenous (IV) fluid therapy to overcome fluid loss, IV dexamethasone (4 mg/day in divided doses), antihistamines, ursodeoxycholic acid 300 mg twice a day, 2% fusidic acid cream topically, and other supportive and symptomatic optimal care was rendered. The patient recovered in a month's time and was discharged. Causality assessment reported this case to be probable ADR as dechallenge and temporal relationship between the drug and the event was established (Fig. 2).

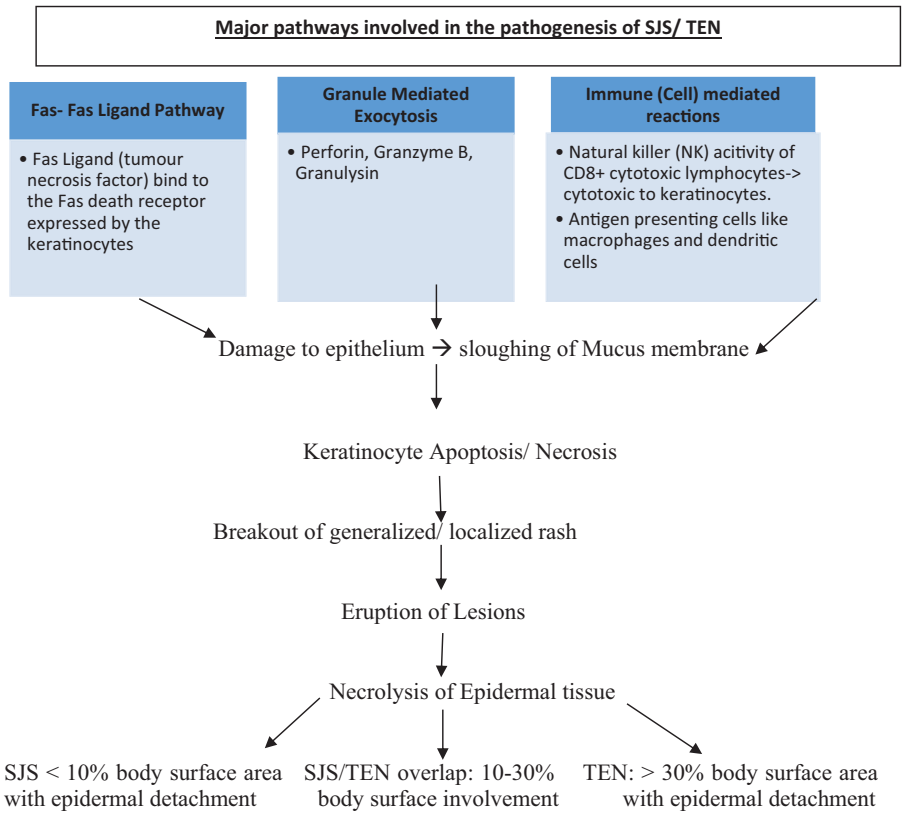
Results and discussion

These case reports of SJS are possible cutaneous ADRs associated with the use of theophylline and meloxicam. These rare unpredictable drug-induced hypersensitivity (type IV) cascade has a T-lymphocyte-triggered initiation phase, where the T-cell-mediated cytotoxic reaction to drug antigens in keratinocytes happens when the drug metabolism fails to detoxify the reactive drug metabolites [4].

Figure 1



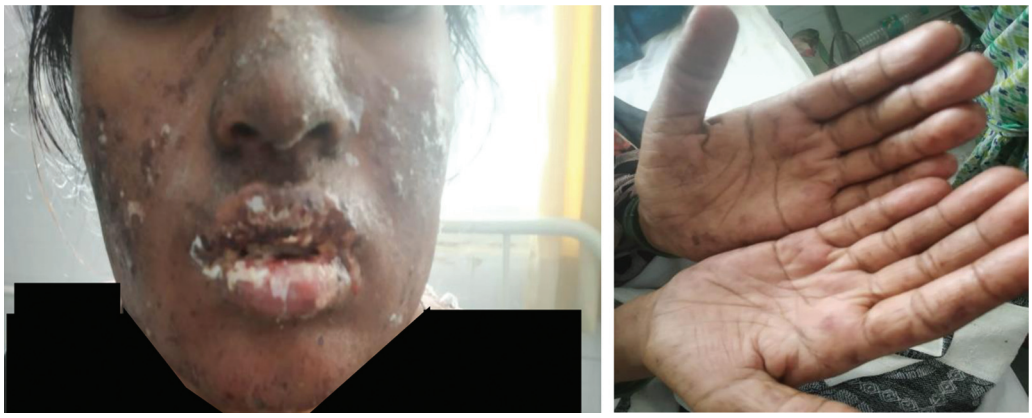
Case report 1: theophylline-induced Stevens-Johnson syndrome.



Symptoms such as fever, malaise, and other nonspecific symptoms developed within a week, followed by breakout of mucosal erythema and lesions over the lip and buccal area, which subsequently underwent central necrosis with vesicle formation. The prognosis of SJS ranges from complete recovery to loss of life. Death in SJS is not rare but can occur in severe secondary infection (HIV being the most common comorbidity in India), gastrointestinal bleeding, and renal failure [5]. Corticosteroids when used in escalating doses may be initially beneficial but is unsafe on long-term as the risk of sepsis and gastrointestinal bleeding is huge. Immunosuppressant like cyclosporine-A may prove effective in reepithelialization and to prevent mucocutaneous lesions [6].

SJS/TEN-specific severity illness score can be expressed as SCORTEN scale (SCORe of Toxic Epidermal Necrosis), evaluating the relevant set of predetermined variables for 24 h after hospital admission. This calculates and predicts the mortality risk by assessing seven independent risk factors namely age (above 40 years), associated malignancy, tachycardia (heart rate more than 120 beats/min), percentage of epidermal detachment, serum

Figure 2



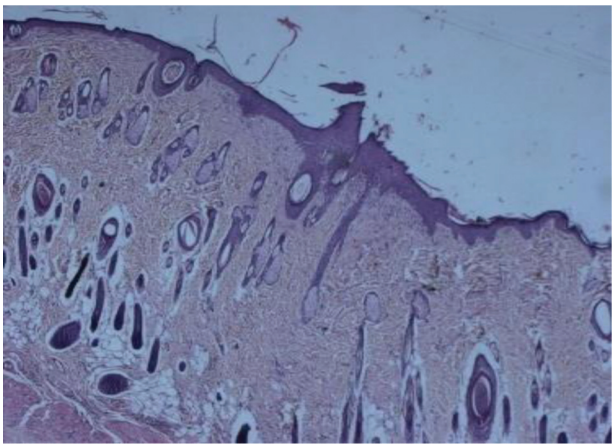
Case report 2: meloxicam-induced Stevens-Johnson syndrome.

bicarbonate (<20 mml/l), serum urea (more than 10 mml/l), and serum glucose (more than 14 mml/l) at admission in hospital. Score of one point for each of the above seven criteria for first 5 days of admission is considered for calculating the SCORTEN score. A SCORTEN score-based mortality prediction (in %) is as follows: score 0-1 (3%), score 2 (12%), score 3 (35%), score 4 (58%), and score 5 (>90%). Drug-induced SJS is a secondary form when the offending drug is taken for a minimum of 8 weeks before the onset of symptoms. The extent of skin sloughing is the primary determinant of SJS mortality, for example, the mortality rate will range from 1 to 5%, when the body surface area sloughing is less than 10%. When body surface area sloughing is more than 30%, the mortality rate falls between 25 and 35%. If the bicarbonate levels are less than 20 mmol/l, then the risk of mortality is 40 times higher [7] (Figs 3 and 4).

Anti-asthma drug, theophylline is a methyl xanthine derivative, which works by inhibiting type III and IV phosphodiesterase, the enzyme that breaks down cyclic AMP in the smooth muscle cells, causing bronchodilation. Theophylline also binds to the adenosine A_{2B} receptor, which blocks adenosine-mediated bronchoconstriction. Theophylline activates histone deacetylase in inflammatory situations to limit transcription of inflammatory genes that require histone acetylation. Theophylline has a narrow therapeutic index (margin of safety) and requires regular monitoring. Adverse effects like headache, nervousness, nausea, dyspepsia, tremors, palpitation, and diuresis are seen with therapeutic doses of theophylline [8].

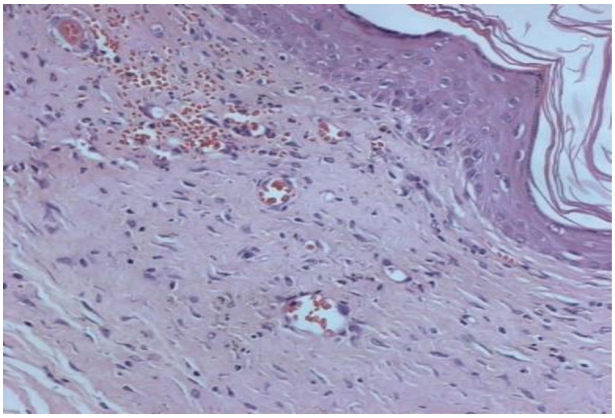
Gene expression analysis of blister fluid cells and fluid from patients with SJS has recently identified secretory granulysin (a cationic cytolytic protein secreted by Cytotoxic T lymphocytes (CTLs), Natural Killer (NK) cells, and Natural Killer T-Lymphocytes (NKT) cells) as a key molecule responsible for the induction of keratinocyte death in SJS. CD8 T cells as well as the cytolytic molecules FasL and granulysin are key players in the pathogenesis of SJS [9]. Yun *et al.* [10] reported recently that lactate dehydrogenase may be an additional useful parameter in the evaluation of disease severity. SJS/TEN is thought to be a type IV hypersensitivity reaction, in which a drug or its metabolite stimulates cytotoxic T cells and helper T cells. The HLA system plays an important role in the pathogenesis of SJS, as some drugs may bind directly to the HLA complex and cause self-reactivity due to the drug-modified HLA-peptide repertoire [11] Meloxicam, an analgesic, inhibits prostaglandin synthetase (cyclooxygenases 1 and 2) enzymes, resulting in lower prostaglandin production, which produces painful inflammatory symptoms. Sensitization of neuronal pain receptors by the inhibition of prostaglandins results in analgesic and anti-inflammatory effects. Meloxicam is a preferential COX-2 inhibitor, which causes gastrointestinal bleeding and perforation on long-term use [12].

Figure 3



Epidermal necrosis with hyperplasia with dermal inflammation.

Figure 4



Severe angiogenesis (more blood vessels formation) near the epidermal and dermal regions of the site of normalization of wound.

Conclusion

It is concluded that the medications theophylline and meloxicam were responsible for causing SJS in these patients, based on clinical manifestations and temporal association. Hence, theophylline and meloxicam should be added to the list of possible drugs that cause SJS. A reliable biomarker for patients presenting with SJS is the need of the hour. Withdrawing the offending drug as soon as possible

and initiating supportive care is a critical first step. Early detection and diagnosis of SJS, as well as treatment with systemic steroids, supportive care, and medicines are found to be effective in the overall management of these patients.

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Conflicts of Interest
There are no conflicts of interest.

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