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Case Report

A case series of cefixime induced Steven's Johnson Syndrome

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ABSTRACT

Drug induced adverse reactions are a major health problem. Drug hyper sensitivity reactions manifest themselves in many diseases, of which some are very severe. The most common allergic reactions occur in the skin. Stevens-Johnson syndrome is mainly caused by drugs (antimicrobials e.g.: penicillin's, sulphonamides and cephalosporin's e.g.: cefixime, antiepileptic's, NSAIDS), infections and also by other risk factors not yet identified. The most common allergic reactions occur in the skin. These reactions ranging from simple pruritic eruptions to potentially life threatening events are a significant cause of iatrogenic morbidity and mortality. Identification of the cause, withdrawal of the trigger and supportive management is crucial to improve the patient state. Despite of all therapeutic efforts, mortality is high and increases with disease severity, patient's age and underlying medical conditions. Survivors may suffer from long-term squeal such as strictures of mucous membranes including severe eye problems.

Keywords: Cefixime, Hypersensitivity reactions, Stevens-Johnson syndrome

INTRODUCTION

SJS is a rare cutaneous, severe, life-threatening drug induced hypersensitivity reaction marked by widespread inflammation of the epidermis ending in necrosis and eventual slouging of the tissue.[1] This syndrome is associated with a rare but serious disorder of the skin, mucous membrane, genitals and eyes due to reaction to a medicament or an infection.[2] It begins with fever and flu like symptoms followed by a painful red or purplish rash that spreads and appearance of blisters. The superficial layers of the affected skin dies, sheds and then heals.[3] Occurrence of SJS is idiopathic or may be attributed to infections such as CMV, mycoplasma.[4] Most common cause of SJS is drug related reactions.[5] First time contact with antibiotics (Sulphonamides, Penicillin's, cephalosporin's e.g.; cefixime) or certain viral infections is more frequent in early life but more common in adults than in children and females are affected more frequently than males whereas polypharmacy may increase the susceptibility to SJS in elderly.[6] SJS is potentially fatal with 10-40% mortality and survivors frequently suffer from permanent complications like eye sequelae.[7] Serious eye issues such as severe conjunctivitis, iritis, corneal blisters, erosions, corneal holes, occurring with this syndrome can be disabling and lead to severe vision loss.[8] Mucus membrane of oral cavity and gastrointestinal tract are typically inflamed.[9] Complications include

dehydration, sepsis, pneumonia and multi-organ failure.[10] The mortality of SJS have been reported as 1±13 and fatalities had been reported to occur in considerable numbers even after discharge from hospital.[11] The success of treatment depends on early recognition of condition, removal of the causative medicament and intensive supportive care.[12] The primary care should include supportive and symptomatic measures, body temperature control, hydration and electrolyte replacement.[13] Special attention to the airways, prevention of secondary infections, pain control, maintenance of venous access distant from the affected areas, early oral or parenteral nutrition.[14] Skin lesions are treated according to dermatological guidelines.[15] Use of prophylactic antibiotics is not recommended, as it can cause /bring about resistance.[16]

CASE SERIES

Case report 1

An 18 years old female patient, a known case of tuberculoma with seizures, on regular treatment with ATT CAT 1 and antiepileptic's (carbamazepine, levetiracetam) since 4 months came to medicine OPD complaining of severe peeling and discolouration of skin all over the body, ulceration in oral cavity and eyelids. She gave history of having taken 2 doses of tablet cefixime 200mg since 1 day for mild fever which was prescribed at the PHC. After taking the second dose, she had severe burning sensation over extremities, back, front of chest associated with itching and redness. Gradually blisters developed over extremities, abdomen and face. There was peeling and discolouration of skin, Ulcerations in oral cavity, eyelids which evolved overnight. There was a rise in body temperature associated with severe headache.

On examination bullous eruptions and detachment of epidermis on face and extremities, crusts over lips and erosion of mucous membrane inside her mouth were seen. All the on-going treatment was stopped. She was treated with calamine lotion for external application, pulse therapy with injection methylprednisolone (pulse therapy), injection chlorophenaramine maleate, nutritional supplements, hydrated with dextrose normal saline, proton pump inhibitors and ringer lactate infusions. Serum chemistry reviled elevated WBC, Neutrophils, eosinophils and ESR. Skin biopsy showed positive Nikolsky sign. 4 days after, her regular medications were started one by one and there was significant improvement in her health condition by 10 days. Rechallange was not done with cefixime. On causality assessment using Naranjo's causality algorithm was probable.

Case report 2

A 26 year old male came to medicine OPD complaining of high grade fever, oral ulceration, dysphagia and severe myalgia since one day. His medical history revealed that he was prescribed tab cefixime 200mg PO, bid along with tab dolo 650mg, po, tid for toothache. He had taken one dose of each medication at night and had high grade fever, severe headache burning sensation in oral cavity. Early in the morning he noticed red swollen lips and was unable to swallow.

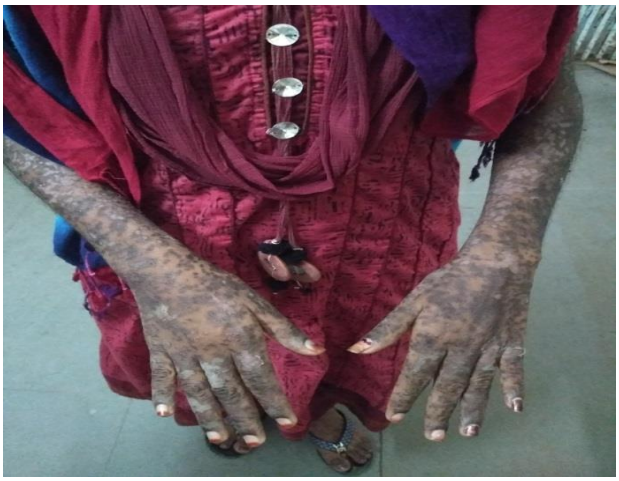

Figure 1: Detachment of epidermis over extremities.

On examination the lips were swollen with flaccid bullae, which turned into haemorrhagic crusts, while the entire oral mucosa and pharynx were denuded. The on-going treatment was discontinued and was prescribed zytee gel for local application, injection Chlorophenaramine maleate, methylprednislone (pulse therapy) and hydrated with fluids (dextrose normal saline). He improved symptomatically. Rechallange was not done with cefixime. On causality assessment using Naranjo's causality algorithm was probable.

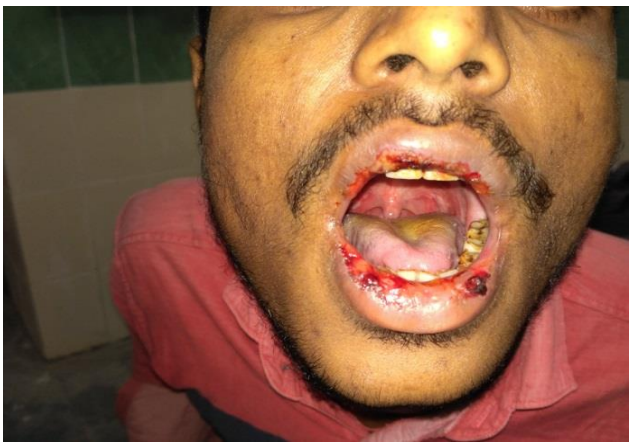

Figure 2: Haemorrhagic crusts over lips.

Case report 3

A 48 year old male had a history of fever and myalgia for which he was prescribed cefixime 200mg po, bd; Paracetamol 650mg po tid. He had taken 2 doses of each and developed rash associated with itching followed by

blistering, peeling and discoloration of skin. Oral cavity was red, inflamed and associated with ulceration.

Intra oral examination revealed ulcerations of the vermilion surface of lips labile mucosa and tongue and palate. The ulcers were haemorrhagic and tender on palpation. Haemorrhagic crusts and erosions were seen on both the lips. Maculopapular rash seen all over the body The on-going treatment was discontinued. He was treated with Zytee gel for local application, injection chlorophenaramine maleate, methylprednisolone (pulse therapy) and hydrated with IV fluids (dextrose normal saline). He improved symptomatically. Rechallange was not done with cefixime. Causality assessment using Naranjo's causality algorithm was probable.

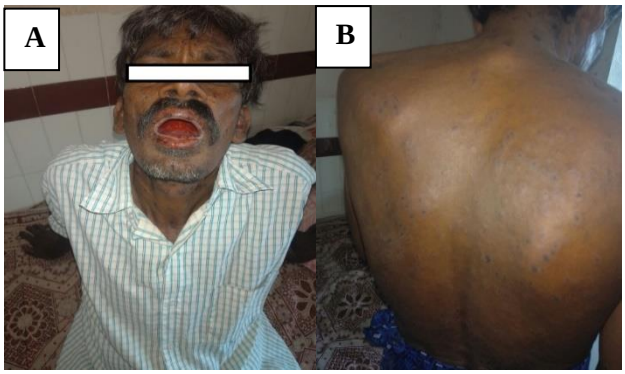

Figure 3: (A) Haemorrhagic crusts and erosions on both the lips; (B) Maculopapular rash over back.

Case report 4

A 19 year old female patient came to medicine female OPD complaining of high grade fever, myalgia, puffiness of face, matted eye lids, swollen lips with blisters. She had a history of mild fever for which she was prescribed tab cefixime and had taken 2 doses. She developed rash over the extremities which progressed to blisters and discoloration of skin, white plaques over the tongue redness and ulceration in oral cavity.

Intra oral examination revealed white plaque candidiasis and crusted lips on ophthalmic examination showed acute conjunctivitis, subconjunctival haemorrhage and matted eyelids, which was associated with watering of eyes and pus discharge was also noted. Her serum chemistry reviled elevated eosinophils, ESR and WBC. Both the drugs were discontinued. she was treated with injection methylprednisolone (pulse therapy), pantoprazole, calamine lotion for external application, fluconazole suspension and hydrated with IV fluids (dextrose normal saline). She improved symptomatically. Rechallange was not done with cefixime. Causality assessment using Naranjo's causality algorithm was probable.

Case report 5

A 25 year old female underwent LSCS 8 days back came to gynaecology and obstritics OPD with fowl smelling vaginal discharge since 2 days, rise in body temperature, myalgia and generalised weakness.

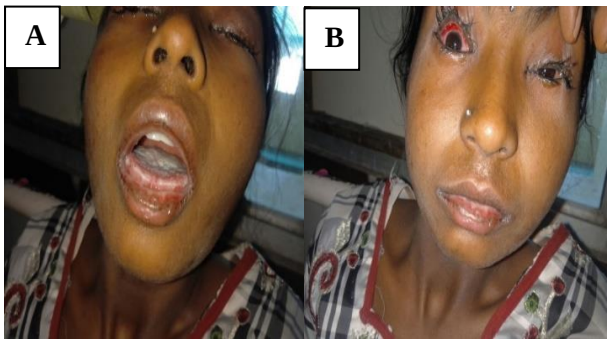

Figure 4: (A) White plaque candidiasis and crusted lips; (B) Subconjunctival haemorrhage and matted eyelids.

On examination erythematous lips, peeling of skin over extremities were noted, Her serum chemistry reviled a significantly many fold rise in eiosinophils and ESR. she was treated a fixed drug combination of cefixime and Azithromycin po bid, Paracetamol 650 po tid, limce po tid. All the on-going treatment was discontinued. She was treated with injection methylprednisolone (pulse therapy) chlorophenaramine maleate, derma dew lotion for eternal application. She was regularly monitored and improved symptomatically. She had used tab azithromycin 500mg on 3 occasions for acute pharyngitis in the past 2 years and no significant adverse events were noted. Rechallange was not done with cefixime. Causality assessment using Naranjo's causality algorithm was probable.

Figure 5: (A) Erythematous lips; (B and C) Peeling of skin on extremities.

Case report 6

A 26 year old male came to dermatology OPD complaining of blisters and peeling of skin over both upper extremities. He had an history of lower respiratory tract infection for which he was prescribed tab. cefixime 200mg po bid, syrup benadryl 7.5ml po tid, tab pan 40mg po od, tab Paracetamol 650mg po tid. Two days after he had oedematous upper limbs, with blisters and peeling of skin. There was a raise in body temperature and myalgia. All the medications which he was taking were discontinued. Lab reports reviled raise in ESR and eosinophil's. He was treated with injection methylprednisolone, calamine lotion for external application, tab limcee. He improved symptomatically. Rechallange was not done with cefixime. Causality assessment using Naranjo's causality algorithm was probable.

Figure 6: Oedematous upper limbs with peeling of skin.

DISCUSSION

Drug hypersensitivity is a major clinical problem. Among many types of drug hypersensitivity, SJS is one of the most serious and life-threatening adverse reaction.[17] The pathophysiological mechanism of SJS is not fully understood. A few individuals have a genetic predisposition to develop such disorders. Slow acetylators are deficient in enzymes involved in the destruction of toxic drug metabolites such as glutathione transferase. Slow acetylators, especially immunocompramised patients and whose liver cannot completely detoxify reactive drug metabolites are at most risk.[18]

In recent past genetic association of few HLA major histocompatibility complex alleles with the occurrence of serious drug reactions had been described. Histopathological hallmark of SJS is wide spread epidermal necrosis due to death by apoptosis of keratinocytes.[19] SJS is denoted by wide spread eruption of macules, papules which eventually lead to skin necrosis, sloughing and has idiopathic illness. The disease occurs when a drug metabolite damages the liver and the organ responsible for storage of vitamin A, causing free retinoid molecules to spill into circulation creating an acute systemic Vitamin A toxicity.[20]

The most prevalent molecule found in SJS blisters is a cytotoxic protein, Granulysin produced in massive quantities by both $CD8^+$ T-Lymphocytes and Natural Killer cells. Granulysin acts as a cytokine for destructed retinoid molecules and is responsible for keratinocyte apoptosis seen in SJS.[21] Involvement of cytotoxic CD 8^+ T cells and NK cells suggests that IL-15 is critical in their development, survival and function .IL-15 is a pleiotropic cytokine produced by masts cell types, promotes T-cell, NK-cell responses and acts as a chemoattractent.[22] Stimulates T-cells to produce proinflamatory cytokines to increase their cytotoxicity, activates dendritic cells and macrophages resulting in increased antigen presentation which drive the adaptive response.[23] Keratinocytes regress, the epidermis becomes detached from the dermis ending in tissue necrosis and sloughing.[24]

SJS/TEN has been observed with more than 100 drugs with common culprits being antimicrobials, antiepileptics and NSAIDs.[25] They increase circulating retinoid levels either through hepatic release as a result of liver injury or through the inhibition of metabolism which leads to higher circulating retinoid derivatives such as retinoic acid, a powerful cell-lysing agent.[26] SCORTEN use seven independent risk factors to predict the risk of death: Age, malignancy, heart rate, epidermal detachment, serum urea, glucose and bicarbonate at the time of admission.[27]

Diagnosis relies on clinical symptoms and histopathological features. Typical clinical signs include areas of erythematous and livid macules of skin on which a positive Nikolsky sign can be induced by mechanical pressure leading to epidermal detachment and development of blisters.[28] on histopathological examination, there is a widespread necrotic epidermis involving all layers. Cultures of blood, urine and skin can reveal the agent of the underlying suspected infection. Serum levels of TNF-α, IL-2, IL-6 and C - reactive protein receptors are typically elevated in these patients.[29]

Histological workup of immediate cryosections or conventional formalin –fixed sections of the skin reveals necrosis in all layers of epidermis caused by apoptosis of keratinocytes and epidermal detachment.[30] Rechallange was not done on ethical grounds. Causality assessment of adverse drug reaction obtained as per WHO-UMC criteria and Naranjo's ADR scale were categorised as probable reaction due to cefixime.[31,32]

Management includes immediate withdrawal of causative drugs. Maintenance of an ambient body temperature, proper fluid-electrolyte balance and maintenance of strict aseptic environment are crucial.[33] Coverage of denuded skin with paraffin gauge. Medical management includes steroids, imunomodulaters.[34] Surgical management includes debridement and coverage with non-adherent cutaneous dressings.[35]

CONCLUSION

Previous studies of Stevens Johnson syndrome have consistently shown that early withdrawal of the offending agent is imperative in improving patient survival. Due to high risk of mortality management of patients with SJS requires rapid diagnosis, evaluation of the prognosis using SCORTEN, rapid identification and interruption of the culprit drug and specialised supportive care. In this study the trigger was most often removed at the time of hospital admission or at the time of diagnosis in the hospital. As such, further education for primary care physicians and patients in recognizing the early signs and symptoms of Stevens Johnson syndrome is needed. More studies and registry system for SJS is required in India to strengthen the data base to design effective treatment modalities. The clinicians should keep in mind about the safety, affordability, need, efficacy to prescribe the right drug to the right patient by right route in right dose at right time. To improve the quality and efficacy of drug therapy it is necessary to have through understanding of existing patterns of therapy and factors that underlie these patterns. Finally, patients should receive medications appropriate to their clinical needs in right doses that meet their own requirements and at a lowest cost to them.

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