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Case Report

Pharmacology Section

Metolazone Associated Stevens Johnson Syndrome-Toxic Epidermal Necrolysis Overlap

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ABSTRACT

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe mucocutaneous disease with high mortality rate. It is characterised by severe necrosis and detachment of the epidermis. Drugs are the most common triggering agent for SJS/TEN. These are commonly reported with the use of aromatic antiepileptics, antiretrovirals, allopurinol, NSAID'S and sulfonamide antibiotics. Non antibiotic sulfonamides rarely cause SJS/TEN. Metolazone is a well known diuretic and is extensively used by clinicians. Although this drug is in market for last several decades, no case of SJS/TEN has been reported till date. We report a rare case of metolazone induced SJS/TEN overlap in a 55-year-old lady.

Keywords: Naranjo Probability Scale, SCORTEN score, Thiazide diuretic

CASE REPORT

A 55-year-old lady came to our hospital with complaints of multiple blistering skin lesions with ulcerations over the lower abdomen, groin and lower back region for the last 2 days which was associated with pain and low grade fever. She was a diagnosed case of hypertension, ischemic heart disease and hypothyroidism, for which she was on regular medications from a cardiologist. Her medications included aspirin, statins, ramipril, metoprolol, thyroxine and torsemide. She was on these medications for last four years and oral Metolazone tablet (5 mg once daily) was added by her cardiologist a week back for refractory pedal oedema. There was no history of similar illness in the past and was tolerating all her medications well.

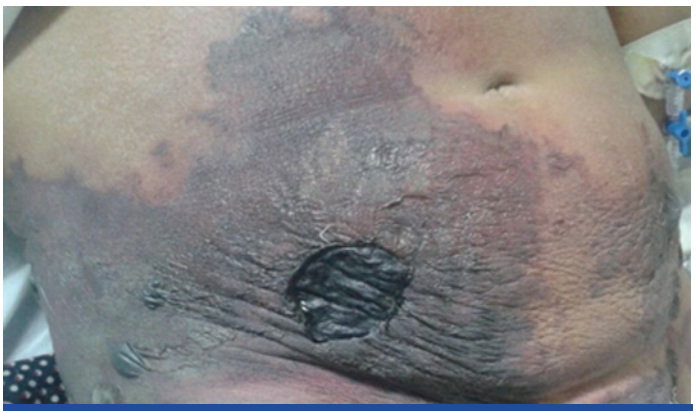
On examination her Pulse rate was 126/min, Blood Pressure-96/70 mm Hg, Respiratory rate-20/min. She was febrile with a temperature of 38.6 degree Celsius. She had bilateral pitting pedal edema and Jugular Venous Pressure (JVP) was significantly raised. Cardiovascular examination was normal but she had bilaterally basal fine crepitations on auscultation of lung fields.

Her skin lesions were irregular erythematous maculo-papular rashes with blister formation and superficial skin excoriation with ulcerations over lower abdomen, groin and lower back and perineum regions [Table/Fig-1,2]. A tangential mechanical pressure on the erythematous areas induced epidermal detachment suggesting that Nikolsky sign was positive. Skin lesions were involving 10-30% of body surface area. The conjunctiva was congested and there were few erosive lesions over the lips. During her hospital stay the blisters ruptured with raw ulceration causing extensive skin denudation. The Naranjo adverse drug reaction probability scale score was 5, indicating a probable relationship between metolazone and SJS/TEN. A diagnosis of Metolazone induced SJS/TEN overlap syndrome was made with a SCORTEN prognostic score of 5.

Haemogram showed a Total leucocyte count of 16,000/cumm with 88% neutrophils and an ESR of 50 mm/h. Renal function test were deranged with urea of 160mg/dl and creatinine of 3.5mg/dl. Liver function tests and Serum elecrolytes were within normal limits. Repeated blood and urine cultures were sterile. A 2D Echocardiography showed an Ejection Fraction of 30% with global hypokinesia of left ventricle. Metolazone, which was the likely culprit drug in this case was immediately stopped. Intravenous fluids were given to prevent dehydration and to maintain adequate urine output. Broad spectrum antibiotics were added to prevent secondary bacterial infection. A non adhesive wound dressing was done over the raw areas and sulfa containing topical medications were avoided. Managing SJS/TEN in this patient was a difficult as the critical element of management of SJS/TEN is giving intravenous fluids which in our case were a challenging task as the patient had congestive heart failure. Patient succumbed to her illness on sixth day of admission due to sepsis and septic shock.

DISCUSSION

Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are acute onset, life threatening mucocutaneous disease. SJS and TEN are an immune mediated hypersensitivity reaction



[Table/Fig-1]: Maculo-papular rash present over lower abdomen with few blister formation.

[Table/Fig-2]: Extensive skin excoriation with ulceration over lower back.

occurring after exposure to certain medications and are believed to be part of the same disease spectrum [1]. Based on percentage of Body Surface Area (BSA) involved, patients are classified into three groups. SJS has less than 10 percent BSA involved; SJS-TEN overlap has 10-30 percent BSA involved and term TEN is used when more than 30 percent BSA is involved. The percentage of body surface area involved is an important prognostic factor in SJS/TEN syndrome [2]. SJS, TEN and SJS-TEN overlap affects almost 2-7 patients per million people per year [3].

After 1-3 weeks of starting the causative medication, prodromal symptoms of fever, cough and malaise develops and is followed by development of mucocutaneous lesion. The skin lesion starts as erythematous macule with purpuric centres and these lesions first appear on face, neck and trunk before involving other areas. As disease progresses, vesicles and bullae are formed leading to sloughing of skin in few days. Nikolsky sign may be positive which is characterized by extension of blister and separation of epidermis when pressure is applied on either affected area or adjacent normal area [4,5]. Mucous membranes are affected in more than 90% of patients with SJS or TEN and can precede skin lesions. Ocular and urogenital involvement is also commonly reported. The acute phase of SJS/TEN lasts 8–12 days and is followed by wound healing and reepitheliazation which usually requires two to four weeks.

Diagnosis is clinical and there are no universally accepted diagnostic criteria for SJS/TEN. A history of drug exposure or illness precedes the onset of prodromal symptoms and classical mucocutaneous lesions. Skin biopsy is not required routinely for diagnosis but it helps in excluding other conditions that mimics SJS/TEN.

The management of SJS and TEN is conservative. The culprit drug should be stopped immediately and complications are managed. The patient should ideally receive treatment at a burns or intensive care unit as it improves prognosis [6]. SCORTEN score is a useful prognostic scale for predicting outcome in these patients [7]. The supportive care includes fluid and electrolyte management, wound and ocular care, nutritional support, prevention and treatment of secondary infections. Although many immunosuppressants like intravenous immunoglobulins (IVIG), steroids, cyclophosphamide, cyclosporine and TNF inhibitors have been used in clinical practice but more evidence are needed before they can be recommended as standard therapy [8].

SJS and TEN have a high overall mortality rate of 25%. Mortality rate for SJS is 10% and almost 40% for TEN [2]. The common causes of death are sepsis with multiple organ failure. There could be long term ocular, oral, dermatological, and pulmonary complications amongst the survivors. The re-exposure of culprit drug could be fatal and the survivors should be educated to avoid these medications in future.

Drugs are the most common trigger for SJS/TEN followed by *Mycoplasma pneumoniae* and cytomegalovirus infections [9]. Drugs at high risk of causing SJS/TEN are allopurinol, antibacterial sulfonamides, aromatic anticonvulsants, and oxicam NSAID's [10]. The risk of SJS/TEN is highest within 8 weeks of drug exposure. Naranjo Probability Scale is a set of questionnaire commonly used to establish a causal relationship between a suspected drug and Adverse Drug Reaction (ADR). Based on score calculated, ADR is considered definite when score is 9 or more, probable if 5-8, possible if 1-4 and doubtful if 0 or less [11].

Metolazone is a thiazide like diuretic, used frequently in treatment of congestive heart failure and chronic kidney disease. Metolazone acts on distal convoluted tubules of nephron where it inhibits sodium chloride symporter, resulting in loss of sodium and water in urine. It is the only diuretic in thiazide group which can act even when the Glomerular Filtration Rate (GFR) is less than 30 ml/min. It is a potent diuretic and is commonly used with loop diuretics for refractory oedema. Since metolazone is a sulfonamide, it can trigger an adverse drug reaction like SJS and TEN. The pathogenesis is not completely understood and is believed to be immune mediated in susceptible hosts. Several studies have demonstrated presence of CD8/CD4 T cells and several cytokines like (IL-6, TNF alpha, Fas-L) in skin biopsy specimen from SJS/TEN patients [12,13].

CONCLUSION

All healthcare professionals should be aware of this possibility and such an event should be recognized immediately. Early discontinuation of the culprit drug and management of complications can decrease mortality and long term sequelae. This case report should alert physicians prescribing Metolazone about this life threatening condition.

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