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Case Report

Dermatology Section

Carvedilol Induced Toxic Epidermal Necrolysis: A Rare Case Report

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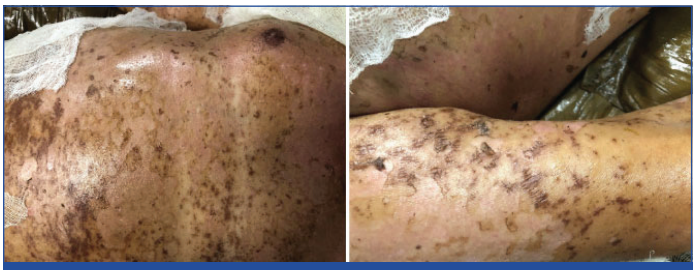
ABSTRACT

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe, life threatening immunologically mediated, mucocutaneous, Adverse Drug Reactions (ADR) associated with high mortality which requires immediate medical care. Carvedilol is a non selective adrenergic blocker used for the therapy of heart failure with hypertension and left ventricular dysfunction following Myocardial Infarction (MI) in clinically stable patients. Hereby, authors report of a 69-year-old male, with a history of MI and hypertension, who received Carvedilol at a dose of 75 mg daily and four days after the first dose of carvedilol, patient presented with erythematous maculopapular rash on face, trunk and limbs with fever up to 38°C. Skin biopsy from one of the fresh lesions showed apoptotic keratinoctyes, subepidermal cleft and monocytic infiltrate in the dermis and the findings were compatible with the diagnosis of TEN. Early recognition and cessation of the drug is of prime importance along with apt treatment and supportive care.

Keywords: Adrenergic blocker, Steven Johnson syndrome, Type IV hypersensitivity

CASE REPORT

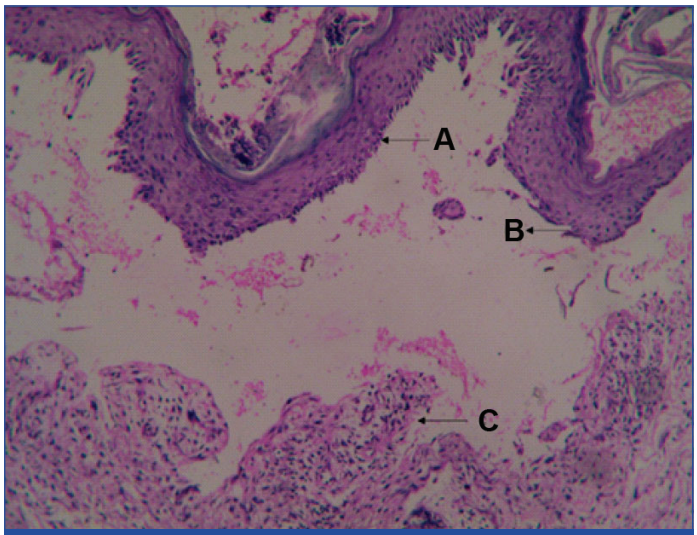
A 69-year-old male with a history of Myocardial Infarction (MI) and hypertension five years back received aspirin at a dose of 75 mg daily, isosorbide mononitrate at a dose of 30 mg twice daily and telmisartan as an antihypertensive at a dose of 40 mg daily by a general physician. Given the lack of response to treatment, carvedilol at a dose of 75 mg daily was added in the regimen by the physician. After four days, the first dose of carvedilol, patient presented with erythematous maculopapular rash on face, trunk and limbs with fever up to 38°C. On physical examination, coalescing dusky red macules covering more than 60% of his body surface area was observed with blisters and detachment of sheets of necrolytic epidermis over his nape of neck and back [Table/Fig-1,2]. Mucocutaneous involvement in the form of erosions over lips and flaccid bullae over the scrotum was noted. Through second week, flaccid blisters and detachment of necrolytic epidermis over his chest and back was observed.



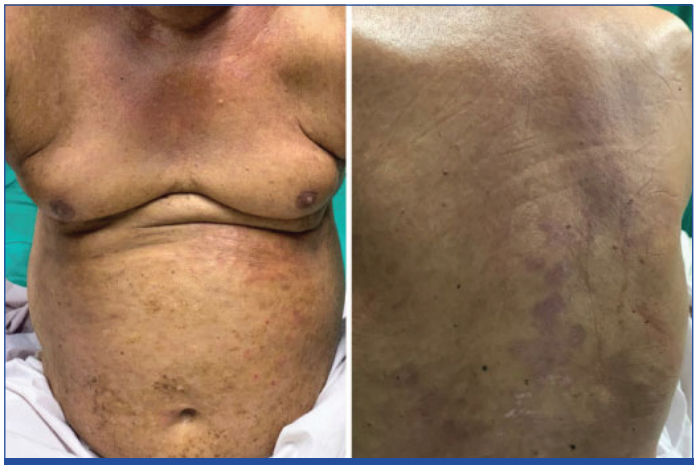
[Table/Fig-1,2]: Showing coalescing dusky red macules covering more than 60% of body surface area with detachment of sheets of necrolytic epidermis. (Images from left to right)

The patient was immediately hospitalised to maintain fluid and electrolyte balance. On admission, his complete haemogram, serum biochemistry including urinalysis was done. Serum urea was elevated (48 mg/dL). SCORTEN scale (SCORe of Toxic Epidermal Necrosis) was applied (69 years, heart rate 110 beats per minutes, initial surface of epidermal detachment was 5%, urea was 48 mg/dL, glucose was 343 mg/dL, bicarbonate was 35.0 mEq/L). With a SCORTEN 4, the probability of mortality predicted was 58% [1]. Skin biopsy from one of the fresh lesions showed apoptotic keratinoctyes, subepidermal cleft and monocytic infiltrate in the dermis and the findings were compatible with the diagnosis of Toxic Epidermal Necrolysis (TEN) [Table/Fig-3].

When a detailed history revealed the causative drug to be carvedilol, immediate cessation of the drug was initiated. Patient was started on supportive treatment in the form of intravenous fluids and antibiotics. Patient was treated with oral cyclosporine (3 mg/kg) 300 mg in a day in divided doses for initial 10 days and then tapered to 200 mg per day. After two weeks, there was resolution of the lesions with no complaints of new lesions over body [Table/Fig-4,5]. At the end of third week, re-epithelisation of skin was achieved with



[Table/Fig-3]: Showing apoptotic keratinocytes (A), subepidermal cleft (B) and monocytic infiltrate in the dermis (C).



[Table/Fig-4,5]: Showing resolutions of lesions after successful treatment. (Images from left to right)

normalisation of renal function parameters and hence the patient was discharged.

DISCUSSION

The Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe, life-threatening immunologically mediated, mucocutaneous, Adverse Drug Reactions (ADRs) characterised by apoptosis, as well as detachment of the epidermis and mucous membranes. It is a Type IV hypersensitivity reaction in which elevated Fas ligand, binds to Fas (its receptor of keratinocytes) and induces immense keratinocyte apoptosis [2]. Stevens-Johnson syndrome and TEN are defined according to their degree of skin detachment <10% of body involvement is termed as SJS, 10-30% as overlap SJS/TEN and >30% labelled as TEN [3]. Stevens-Johnson syndrome and TEN are frequently drug related and the most common agents responsible for causing this condition are: antibiotics {sulfonamides (sulfamethoxazole, sulfadiazine, and sulfapyridine, beta-lactams cephalosporins, penicillins, and carbapenems)}, Non Steroidal Anti-Inflammatory Drugs (NSAIDs), allopurinol, antimetabolites like methotrexate, antiretroviral drugs like nevirapine, corticosteroids, anxiolytics like chlormezanone, anticonvulsants such as phenobarbital, phenytoin, carbamazepine, and valproic acid [4].

Carvedilol is a non selective adrenergic blocker used for the therapy of heart failure with hypertension it is preferred in clinically stable patients of left ventricular dysfunction succeeding MI [5].

Kowalski BJ et al., reported a case of a 71-year-old male who was a known case of ischaemic cardiomyopathy and was started on carvedilol. When a titrated dose of 12.5 mg twice a day was initiated, he developed purpuric macules and blisters involving entire skin surface and mucous membrane, the signs and symptoms were compatible with SJS. Immediate cessation of the drug was done and patient was started on Methylprednisolone and IV fluids [6]. Vlahovic-Palcevski V et al., reported a case of TEN after two days of initiation of carvedilol which lead to rapid epidermal necrolysis and fatal outcome, even after withdrawal of the offending drug [7]. Adverse drug reactions are a matter of concern for being one of the leading causes of morbidity and mortality among hospitalised patients. Report suggests that 8% of cases among all hospitalisations are due to ADRs [8]. SJS/TEN presents commonly between four days and four weeks after exposure to the drug [9]. Recognition and early cessation of the drug is of paramount importance. An optimal electrolyte balance should be ensured with monitoring of the vitals. Skin care is based on minimising trauma, use of topical antiseptics and bland emollients [10].

Regarding systemic treatment, oral cyclosporine has gained popularity in the treatment of SJS/TEN due to the suggested role of T-lymphocytes in the pathogenesis of TEN. Cyclosporine inhibits the activation of CD4+ and CD8+ (cytotoxic) T-cells in the epidermis by suppressing interlekuin-2 production from activated T helper cells [11]. Cyclosporine is used in a dose of 3-5 mg/kg body weight, as oral capsules or solution, in divided doses. However, side-effects such as septic complications and severe leukopenia (<1000 cells/mm) should be watched out for. Other systemic modalities include systemic corticosteroids and Intra Venous Immunoglobulins (IVIG).

CONCLUSION(S)

In conclusion, authors report this case owing to it's rarity and high mortality rate. Early recognition and cessation of the drug is of prime importance along with apt treatment and supportive care.

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