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Metolazone Induced Stevens Johnson Syndrome (SJS)

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Abstract: *Stevens Johnson Syndrome (Sjs) Is Characterized By Hemorrhagic Erosions, Erythema And Often Presents As Blisters And Detachment Of The Epidermis Because Of Necrosis. It Is A Type Iv Hypersensitivity Reaction Secondary To Medication Or Infection. Drugs Like Allopurinol, Carbamazepine, Aminopenicillins, Oxicam-Type Of Nsaids, Etc Are At High Risk Of Causing Stevens-Johnson Syndrome. Metolazone,Is A Long Acting Thiazide Like Diuretic. It Potentiates The Action Of Furesomide. Metalozone Induced Sjs Is Rarely Reported.. We Report A Rare Case Of Metolazone Induced Sjs In A 58 Year Old Male Patient.*
Key Words*- Stevens-Johnson Syndrome (Sjs), Mucocutaneous, Metolazone*

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I. Introduction

Stevens-Johnson Syndrome Is A Rare Type Of Skin And Mucous Membrane Disorder Associated With Drug Reactions. Initially Patient Has Generalized Pain Associated With Fever Followed By Red And Purple Skin Rashes Which Cover Almost Entire Skin Surface. Later Blisters Appear Over The Site Of Rashes. This Is Then Followed By Shedding Of Skin Which Signifies Recovery Phase. Drugs That Cause Sjs Include Anti-Gout Medications, Anti-Convulsants, Anti-Psychotics, Diuretics. Sjs Is A Medical Emergency And Should Be Treated Aggressively.

II. Case Report

A 55year Old Male, Known Case Of Chronic Kidney Disease On Irregular Hemodailysis Presented To Us With Volume Overload, Pulmonary Edema And Metabolic Acidosis. He Was Managed With Hemodialysis Which Was Given Regularly 3 To 4 Days, Antihypertensive, Hemetenics, And Torsimide 80mg Bid. In View Of Inefficient Edemas Control Tab Metalozone 5mg Was Added To The Treatment Regimen. Two Days After Adding Metalozone Multiple Skin Lesions With Blistering And Ulcerations Over Anterior Abdomen,Back,Groin And Face Appeared. It Was Associated With Low Grade Fever, Eye And Oral Mucosal Involvement.

His Lesions Were Irregular Erythematous Maculo-Papular Rashes With Superficial Skin Excoriation Over Anterior Abdomen, Back,Groin And Face [Fig-1,2]. Skin Lesions Were Involving 30-50% Of Body Surface Area.There Were Few Erosive Lesions Over The Lips And Conjunctiva Which Were Congested. A Tangential Mechanical Pressure On The Erythematous Areas Induced Epidermal Detachment Suggesting That Nikolsky Sign Was Positive. During His Hospital Stay The Lesions Ulcerated And New Bare Intact Skin Was Formed.

The Naranjo Adverse Drug Reaction Probability Scale Score Was 8 (Table 1), Indicating A Probable Relationship Between Metolazone And Sjs. A Diagnosis Of Metolazone Induced Sjs Overlap Syndrome Was Made With A Scorten Prognostic Score Of 3 (Table 2) Suggesting 35.3% Mortality.

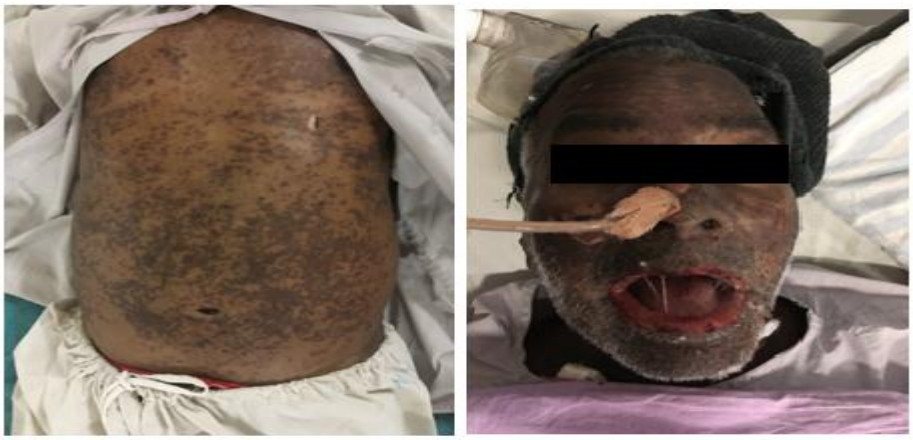

Figure 1 And 2 Showing The Skin Lesions Of Sjs.

Complete Blood Count Showed A Total Leucocyte Count Of 27,700/Cumm With 78% Neutrophils And An Esr Of 56 Mm/H. Renal Function Test Were De-Ranged With Urea Of 210mg/Dl And Creatinine Of 8.5mg/Dl. Liver Function Tests And Serum Elecrolytes Levels Were Within Normal Limits. Repeated Blood And Urine Cultures Showed No Growth.

Metolazone, Which Was Thought To Cause Drug Reaction In This Case Was Immediately Stopped. Iv Fluids Were Started To Prevent Dehydration.Broad Spectrum Antibiotics Were Started To Prevent Secondary Bacterial Infection. A Non Adhesive Wound Dressing Was Done. Major Difficulty In Managing This Patient Was To Maintain Patient's Hydration And At The Same Time Prevent Fluid Overload Due To Non-Functioning Kidneys. Patient Was Put On Daily Hemodialysis Sessions For The Same And Hydration Was Maintained.

Patient Was Also Started On Low Dose Cyclosporine And Tapering Dose Of Corticosteroids. In A Period Of About 10 Days, Patient's Rash Was Improved With New Skin Formation. The Patient Was Continued On Hemodialysis And Patient Was Discharged On 15 Th Day And Is Now On Maintenance Hemodialysis.

Table.1 Adverse Drug Reaction Probability Scale Response In Our Case

Question	**Yes**	**No**	**Do Not Know**	**Score**
1. Are There Previous Conclusive Reports On This Reaction?	+1	0	0	**0**
2. Did The Adverse Event Appear After The Suspected Drug Was Administered?	+2	-1	0	**+2**
3. Did The Adverse Event Improve When The Drug Was Discontinued Or A Specific Antagonist Was Administered?	+1	0	0	**+1**
4. Did The Adverse Event Reappear When The Drug Was Readministered?	+2	-1	0	**0**
5. Are There Alternative Causes That Could On Their Own Have Caused The Reaction?	-1	+2	0	**+2**
6. Did The Reaction Reappear When A Placebo Was Given?	-1	+1	0	**+1**
7. Was The Drug Detected In Blood Or Other Fluids In Concentrations Known To Be Toxic?	+1	0	0	**0**
8. Was The Reaction More Severe When The Dose Was Increased Or Less Severe When The Dose Was Decreased?	+1	0	0	**+1**
9. Did The Patient Have A Similar Reaction To The Same Or Similar Drugs In Any Previous Exposure?	+1	0	0	**0**
10. Was The Adverse Event Confirmed By Any Objective Evidence?	+1	0	0	**+1**
	Total Score:			**8**

Table.2 Scorten Scale In Our Patient

Risk Factors	O	1	**Scores**
Age	<40 Years	>40 Years	**1**
Associated Malignancy	No	Yes	**0**
Heart Rate (Beats/Min)	<120	>120	**1**
Serum Bun (Mg/Dl)	<28	>28	**1**
Detached Or Compromised Body Surface	<10%	>10%	**0**
Serum Bicarbonate (Meq/L)	>20	<20	**0**
Serum Glucose (Mg/Dl)	<252	>252	**0**

III. Discussion

Stevens Johnson Syndrome (Sjs) Is A Rare, Acute Onset And Potentially Life Threatening Skin Reaction, Which Is Almost Always Caused As A Result Of Hypersensitivity Reaction To Certain Drugs.[1] Mechanism For This Reaction Is Still Unclear And Considered To Be Complex, Probably With Some Genetic Link.More Than 200 Drugs Have Been Reported To Cause Sjs.

Symptoms Of Sjs/Ten Start To Appear Within A Few Days Of Drug Exposure And Can Last Upto 1 Month. Initially Patient Develops Prodromal Symptoms (Flu-Like Illness). This Is Followed By Abrupt Onset Of A Tender, Red Skin Erythema Starting On The Trunk And Extending To Face And Limbs In A Matter To Several Hours To A Couple Of Days While Full Extent Is Reached In 4 Days. Skin Lesions Progress From Macular Rashes To Blister Formations. Blisters Then Merge To Form A Thin Sheet Of Skin Which Later Detach Thereby Exposing Red Oozy Dermis. Nikolski's Sign Is Positive In Areas Of Erythema. [2,3]Mucosal Involvement Is Frequently Observed And Is Severe In Most Cases, Usually Affecting More Than Two Mucosal Surfaces; Eyes And Oral Mucosa Being The Most Common Ones[4,5]

Patients Are Classified Into Three Groups With Respect To Percentage Of Body Surface Area (Bsa) Involved. The Term Sjs Is Used When There Is Less Than 10 Percent Bsa Involved; Sjsten Overlap Has 10-30 Percent Involvement And Ten Has More Than 30 Percent Bsa Involvement. [6] Diagnosis Is Clinical With Classical Muco-Cutaneous Lesions And A History Of Drug Exposure. Skin Biopsy Is Not Required Routinely For Diagnosis But It Helps In Excluding Other Conditions Like Staphylococcal Scalded Shock Syndrome(Ssss).

The Line Of Management Of Sjs And Ten Is Usually Conservative. The Causative Drug Should Be Stopped Immediately And Supportive Care Should Be Initiated. The Supportive Care Includes Fluid And Electrolyte Management, Wound Care, Nutritional Support, Prevention And Treatment Of Secondary Infections. Various Immunosuppressants Such As Ivig, Tnf Inhibitors, Cyclophosphamide, Cyclosporine And Steroids Are Being Used In Clinical Practice As An Effective Measure But More Researches Need To Be Conducted Before Standardizing The Treatment Plan. [7]

Cyclosporine (3-5 Mg/Kg/Day) Has Proven To Be A Trend Changing Drug As It Reportedly Reduced Mortality Rate Drastically When Tested Among Patients With Similar Scorten Score. Scorten Score Is A Illness Severity Score Useful To Predict Mortality.[8] Sjs Has A Mortality Rate Of 10% While It 40% In Case Of Ten.[6] The Common Causes Of Death Are Sepsis And Multiple Organ Failure. Long Term Ocular, Oral, Dermatological, And Pulmonary Complications Are Noted Amongst The Survivors. The Re-Exposure Of Causative Drug May Seem Fatal Hence Their Use Must Be Strictly Avoided. Naranjo Probability Scale Is A Tool Used To Establish A Causal Relationship Between A Suspected Drug And Adverse Drug Reaction (Adr). Based On Scores Calculated From A Questionnaire, The Chances Of Occurrence Of Adr Is Determined.Score Of 9 Or More Suggests Definite Adr, 5-8 Suggests Probable Adr, 1-4 Suggests A Possibility, Doubtful If 0 Or Less.[9]

Metolazone Is Aquinazoline-Sulfonamide That Is Considered Along Actingthiazide-Like Diuretic, Hence They Are Used In Chronic Renal Failure. Metolazone Acts On Distal Convoluted Tubules Of Nephron And Causes Diuresis By Inhibiting Sodium Chloride Symporter. It Is The Only Diuretic In Thiazide Group Which Can Act Even At Gfr's Of Less Than 30 Ml/Min. It Is Commonly Used In Addition To Loop Diuretics As A Treatment For Refractory Oedema. Metolazone Being A Sulfonamide Is The Reason For It To Trigger An Adverse Drug Reaction Like Sjs And Ten. The Pathogenesis Is Considered To Be Complex And Is Believed To Be Immune Mediated. Metalozone Specific Cd8+ Cytotoxic Lymphocytes And Several Cytokines Like Il-6, Perforin/Granzyme, Fas-L And Tnf-A Can Be Detected In Skin Biopsy Specimen From Sjs/ Ten Patients.[10,11]

IV. Conclusion

The Possibility Of Sjs Should Force Every Healthcare Professional To Stay Alert To Possible Culprit Medications, And Early Discontinuation And Immediate Management Of The Condition Should Be Practiced To Decrease The Gruesome Mortality Rates. This Case Report Should Remind Physicians Prescribing Metolazone About The Possible Life Threatening Effects In Case Of An Adverse Reaction

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