COTRIMOXAZOLE INDUCED SWEET SYNDROME CASE REPORT A DERMATOLOGICAL EMERGENCY

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doi.org/10.55634/4.2.8

ABSTRACT:

Background: Sweet syndrome is an uncommon immune mediated allergic reaction, presenting with acute pyrexia, leukocytosis and erythematous skin lesions with dense neutrophilic dermal infiltration. SS is seen as adverse reaction to some drugs, microbial infections, inflammatory and autoimmune diseases like inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, Sjogren syndrome, Hashimoto thyroiditis, dermatomyositis and is associated with certain myeloproliferative or haematological neoplasms.

Results: A female, aged 43 years came to the hospital with high fever and erythematous, pus filled plaques and nodules on face, neck, shoulders and extremities, after taking tablet Cotrimoxazole 480mg twice daily for 12 days for urinary tract infection. The diagnosis of Sweet syndrome was arrived upon from the reports of biopsy showing predominant neutrophilic infiltrate and relevant laboratory tests. Treatment included oral prednisone and the symptoms resolved in 2 months.

Conclusion: As the precise aetiology of Sweet's syndrome is still unknown, vigorous efforts must be made to explore the aetiology of Sweet's syndrome for better diagnosis and treatment. Innovative and effective treatment strategies like targeted therapy may be potentially beneficial to such patients.

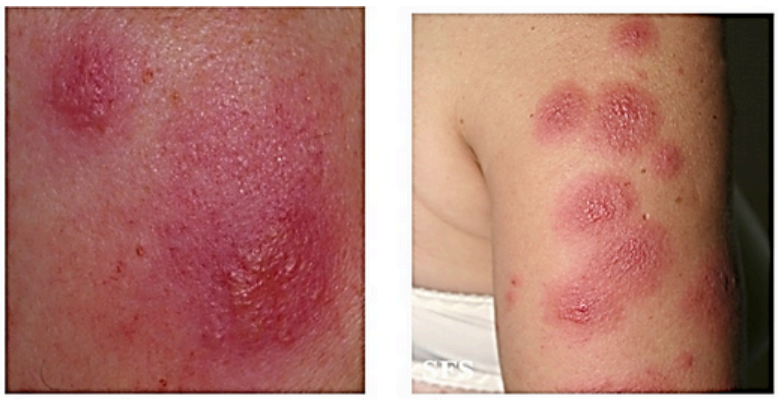

FIG. 1: COTRIMOXAZOLE INDUCED SWEET SYNDROME

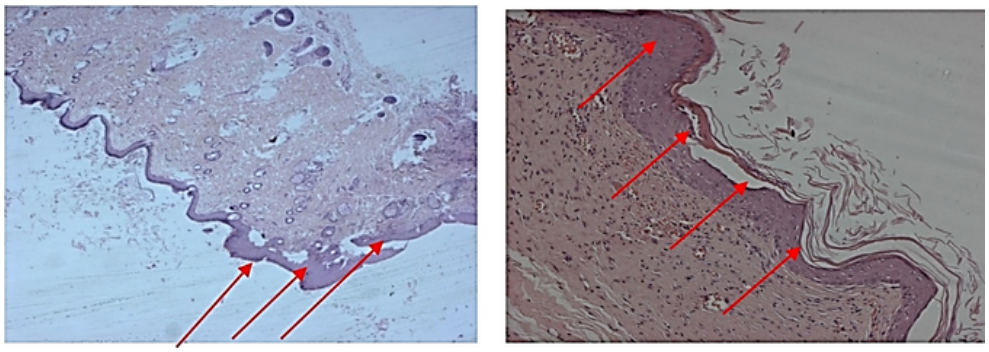

FIG. 2: COMPLETE RE EPITHELIZATION AFTER TREATMENT

BACKGROUND:

Sweet syndrome (SS) also called the acute febrile neutrophilic dermatosis is an rare inflammatory dermatological disorder with typicalsymptoms such asrapid onset of painful cutaneous neutrophilic lesions that are tender, red, swollen and painful, erupting mostly located in the upper dermis of skin of the face, arms, neck, head, trunk along with rapid onset of fever and leucocytosis(1). Dr. Robert Douglas Sweet was the first person to describe this inflammatory condition in 1964 and hence named after him. Co-trimoxazole induced Sweet's syndrome was first described in 1986(2).

SS is an autoimmune disorder, a form of hypersensitivity developed in response to antigens like bacteria or virus or tumour or even some drugs which initiates a cascade of cytokine release. Exacerbation of lesions on exposure to sunlight (photoinduction) and appearance of new, typical skin lesions in otherwise healthy skin (Koebner phenomenon) may be the reason for local skin lesions in SS (3). The pro-inflammatory ultraviolet Bmay recruit and activate more neutrophils along with enhanced release of TNF-α and interleukin-8 (IL-8) (4–6).

Till date, only fewSS cases have been reported and generally has a female predilection with female to male ratio of 4 to 1 (7).

CASE PRESENTATION:

A female of age 43 years, presented to the outpatient department of Dermatology with high grade fever and erythematous, pus filled plaques and nodules on face, neck, shoulders and extremities, after taking tablet Cotrimoxazole 480 mg twice daily for 12 days for urinary tract infection.Skin biopsy and laboratory tests yielded a diagnosis of Sweet syndrome.Acute-phase reactants-C reactive protein, peripheral neutrophils, leucocyte count, erythrocyte sedimentation rate (ESR) was elevated. Dense,diffused neutrophilic infiltrate in dermis with oedema in the papillary dermis was revealed in the biopsy report. The offending drug was immediately stopped (dechallenge). She was treated with oral prednisone 40 mg daily for 2 weeks followed by dose tapering upto 4th week, topical antipruritic. In 2 months her symptoms were resolved. Rechallenge was not done. According to WHO scale of ADR causality assessment, this Cotrimoxazole induced SS was found to be probable case (Fig-1).

DISCUSSION:

Sweet syndrome is classified into three further groups:

Classical Sweet syndrome (CISS)- Idiopathic- may be seen in conditions like upper respiratory infections, gastrointestinal infections or pregnancy (first or second trimester)(8–9).

Malignancies associated Sweet syndrome (MASS)- is seen inspecific cancers like acute myeloid leukemia (AML)(10).

Drug induced Sweet syndrome (DISS)- occurs with drugs like co-trimoxazole, minocycline, abacavir, furosemide, hydralazine, Ibuprofen, Tretinoin or all-trans retinoic acid (ATRA) and drugs which stimulate production of G-CSF (granulocyte colony-stimulating factor). DISS occurs after exposure to the offending drug as well as re-exposure and after the withdrawal of the drug, resolution occurs with or without the use of steroids (1).

The pathogenesis of SS is said to be multifactorial. Endogenously G-CSF levels were raised in multiple cases of SS, with elevations in serum concentrations correlating

with clinical disease severity. The growth factor, G-CSF stimulates proliferation, differentiation and maturation of leucocytes which then attaches to the upper dermis of the skin (11–12).The exogenous G-CSF use may intensify the causative role of G-CSF in SS further as seen in drug-induced SS. Cytokines interleukin IL-17, IL-1b are involved in SS and inflammasome may be activated. Reports of rare extra cutaneous manifestations involving the central nervous system, internal organs, musculo-skeletal system, ophthalmic manifestations like corneal ulceration, raised intra ocular pressure (IOP) are also noted(13–15). Relapse may occur in around 30–50% of people with SS, especially in malignancy cases. SS is found to be mostly common in women of age group (30–50) years and the genetic marker associated is HLA-B54 (7).

DIAGNOSTIC CRITERIA FOR DRUG INDUCED SWEET'S SYNDROME (16):

Sudden onset of painful, tender, erythematous plaques or nodules, distributed asymmetrically.

Histopathological hallmark is the dense neutrophilic infiltrate in the dermis. Leukocytoclastic nuclear debris is seen interstitially, and papillary dermal oedema is common.

These are the two major significant findings in SS.

Fever - a temperature greater than > 38°C (100°F).

Established temporal association between drug intake (cause) and clinical presentation (effect), or recurrence after rechallenge.

Dechallenge positive: temporally-related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids

Minor criteria must include at least two of the four following:

Vaccination, post infection of the upper respiratory or gastrointestinal tract often precedes SS, and may be associated with pregnancy, any inflammatory disease or certain malignancies.

Patient's response to systemic corticosteroid therapy is excellent.

Abnormal laboratory values at presentation (three of four of the following):

Erythrocyte sedimentation rate > 20 mm/h

Positive C-reactive protein.

>8,000 leukocytes per micro liter

>70% neutrophils

Skin biopsy may be sent to laboratory for further evaluation and final confirmation after a clinical examination. Dense inflammatory infiltrates in the superficial dermis show poly morphonucleocytes, lymphocytes and oedema of the dermal papillae is remarkable (17) (Fig. 2- B).

TREATMENT:

Categorically, if SS is not falling under CISS or MASS, self-limiting and the response to steroid treatment is notable. Treating the underlying cause may resolve the symptoms. In drug induced SS, timely identification and removal of the offending agent is beneficial but must be treated with the golden standard steroid therapy systemically. Oral prednisone course is started for2 to 4-week with gradual dose weaning. To start with a daily dose of 40–60 mg is administered. Intralesional steroid injections and topical corticosteroids may be useful if lesions are limited (Fig. 2- A). In recurring SS after tapering steroid, many steroid-sparing drugs such as potassium iodide, colchicine, dapsone, isotretinoin, methotrexate, doxycycline, indomethacin, chlorambucil, and cyclosporine were tried and found efficacious. Ensure patient compliance, avoidance of drug interactions while treating SS patient (7, 18, 19, 20).

CONCLUSIONS:

SS is a rare inflammatory condition of reactive dermatosis withunknown etiopathogenesis and is commonly steroid-responsive.With prompt diagnosis and adequate medical intervention, the SS lesions resolve without scarring. DISS was most often associated with administration of G-CSF. Futuristic revolutionary discovery of immune mediated pathways associated with sweet syndrome may have additional implications in elucidating several other autoimmune disorders.Therapies targeting interleukin IL-17, IL-1b and activated inflammasome, adsorption apheresis of granulocyte and monocyte may be utilized as novel approaches in SS management in the future(1).Awareness of SS and DISS among clinicians must be crucially raised. Haematologist or oncologist must think of the possibility of Sweet's syndrome to be included in a differential diagnosis in patients with fever and abrupt cutaneous lesions.

ABBREVIATIONS

SS - Sweet syndrome
IL- Interleukin
ESR - erythrocyte sedimentation rate
CISS - Classical Sweet syndrome
MASS – Malignancies associated Sweet syndrome
DISS - Drug induced Sweet syndrome
ATRA - All-trans retinoic acid
G-CSF - granulocyte colony-stimulating factor

DECLARATIONS

1. Funding - No Funding received
2. Conflicts of interest/Competing interests - None to declare
3. Ethics approval - IAEC/SRMC/2022-23/02
4. Consent to participate - Taken consent from the patient
5. Written Consent for publication – Taken consent for publication of their images
6. Availability of data and material (data transparency) - Not applicable
7. Code availability - IAEC/SRMC/2022-23/02
8. Authors' contributions

All authors have done equal contributions in preparing and revising this manuscript content. All authors approved the final manuscript. The following case report article is not presented at any conference and not published elsewhere. Dr. K. Naga Vishnu—concept, design of the study acquisition of the data, and analysis. Anjaly Mary Varghese—drafting the article or revisingit critically for important intellectual content and manuscript final review. (Dr). Praveen Kumar Uppala—design of the study, the conception, acquisition of the data, and analysis interpretation of the data (corresponding author). U.Upendrarao—design of the study, the conception, and acquisition of the data. Dr. S. VenkataSaibaba—intellectual content and design of the study acquisition of the data.Murali Krishna—acquisition of the data and literature. The authors read and approved the final manuscript.

ACKNOWLEDGEMENTS:

I acknowledge my great thanks to NCC-PvPI, Indian Pharmacopeia Commission, Ghaziabad and Santhiram Medical College & General Hospital, Nandyal for their continuous support and cooperation.

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