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Trimethoprim - Sulfamethoxazole Induced Sweet Syndrome: A Case Report

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ABSTRACT

Sweet syndrome (SS) also called as acute febrile neutrophilic dermatosis, is a rare inflammatory infectious skin reaction characterized clinically by tender, erythematous papules or plaque commonly appearing on the upper limbs, trunk, and head and neck. It is usually accompanied by fever and an elevation in the erythrocyte sedimentation rate (ESR), C- reactive protein. SS is classically triggered by infections, inflammatory bowel disease, pregnancy, malignancy or due to the administration of an associated drugs. Drug induce sweet syndrome (DISS) an uncommon subtype of SS. Drugs like antiepileptics like carbamazepine, diazepam, antibiotics like trimethoprim-sulfamethoxazole (TMP-SMX), minocycline, nitrofurantoin, norfloxacin, ofloxacin, contraceptives, non-steroidal anti-inflammatory drugs (NSAIDS) (celecoxib and diclofenac) and granulocyte – colony stimulating factor are the most common culprit. In this case, the patient was presented with oedematous and pustular eruption of nose with a rapid extension to the face, neck, upper trunk and the limbs which developed after taking TMP-SMX for 10 days accompanied with fever (42ºC) and cough. Laboratory test disclosed elevated WBC with notable increase in polymorphonuclear cells, elevation of ESR (96mm/h), C-reactive protein (85ng/l, normal <5) and α-2-globulin (10g/l, normal <8). All these presentations clearly indicated that the patient is having DISS as per Walker and Cohen criteria for SS. TMP-SMX was discontinued upon which the lesions started to disappear. Clinical pharmacist must be more aware about the usage of TMP-SMX especially in immune compromised patients.

Keywords: Drug induced sweet syndrome, Trimethoprim-sulfamethoxazole, Neutrophilic infiltration, Corticosteroids, oedematous papules,

INTRODUCTION

Sweet syndrome (SS), or acute febrile neutrophilic dermatosis, is an inflammatory, non- infectious skin reaction characterized clinically by tender, erythematous papules or plaque commonly appearing on the upper limbs, trunk, and head and neck. It is usually accompanied by fever and an elevation in the ESR, C- reactive protein. SS is classically triggered by infections, inflammatory bowel disease, pregnancy, malignancy or due to the administration of an associated drugs.[1] Several variants have been described both clinically and histopathologically. Classification of SS include classic SS, malignancy associated and drug induced. Drug induce sweet syndrome (DISS) an uncommon subtype of SS. Drugs like antiepileptics like carbamazepine, diazepam, antibiotics like trimethoprim-sulfamethoxazole (TMP-SMX), minocycline, nitrofurantoin, norfloxacin, ofloxacin, contraceptives, NSAIDS (celecoxib and diclofenac) and granulocyte – colony stimulating factor are the most common culprit. [2] The cellular and molecular mechanisms involved in sweet's syndrome have been difficult to elucidate due to the large variety of conditions leading to a common clinical presentation. The pre-existing myeloid dysfunction and disruption in normal

cytokine and stimulating factors provide the environment necessary for aberrant neutrophil activation and inflammation. In classic and drug induced SS, an inciting stimulus such as an antigen in an individual with a genetical predisposition likely creates a similar pro-inflammatory state resulting in SS. The first line treatment for SS includes corticosteroids (prednisone 0.5-1mg/kg/day) and other agents such as potassium iodide or colchicine. Second line agents include indomethacin (150mg/day for the first week and 100mg/day for two additional weeks), clofazimine, cyclosporin and dapsone. [3] The effectiveness of these medications with differential mechanism of action highlights the role of both adaptive and innate cells in the pathogenesis of SS. In this report the diagnosis of sweet syndrome is done by using Walker and Cohen criteria (Table 1) and all the criteria had met for diagnosis. [4] A strikingly robust presentation of trimethoprim -sulfamethoxazole (TMP-SMX) induce SS is discussed.

Table 1: Walker and Cohen criteria for diagnosis of drug – induced sweet syndrome.

CRITERION NO	CRITERIA
1	Abrupt onset of painful erythematous plaques or nodules
2	Histopathologic evidences of a dense neutrophilic infiltrate without evidences of leukocytoclastic vasculitis
3	Pyrexia >38ºC
4	Temporal relationship between drug ingestion and clinical presentation or temporally related recurrence after oral challenge
5	Temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.

CASE DESCRIPTION

A female patient, aged 42-year-old came to S.S.I.M.S & RC, Davangere, Karnataka with an oedematous and pustular eruption of nose with a rapid extension to the face, neck, upper trunk and the limbs. The patient was administered trimethoprim-sulfamethoxazole (TMP-SMX) in a dose of 400mg/80mg orally every 12 hrs for 10 days for urinary tract infection 10 days prior to the condition. At presentation, physical examination revealed scattered erythematous patches, pustular and blisters localized on the scale, upper back, chest and palms (Fig 1). She had fever (42ºC) and cough. Laboratory test disclosed elevated WBC with notable increase in polymorphonuclear cells ($20.5x\ 10^{-3}$ /mm^3) [upper normal limit ($7.0\ x10^{-3}$)], an inflammatory syndrome with elevation of ESR (96mm/h), C-reactive protein (85ng/l, normal <5) and α-2-globulin (10g/l, normal <8). Blood culture was negative for bacteria and urine culture was contaminated by vaginal flora. Microscopic examination of cutaneous lesions revealed a prominent neutrophilic infiltrate of the dermis without vasculitis consistent with sweet syndrome. Dramatic improvement was observed after TMX-SMX was withdrawn. And the lesions started re-appearing once TMP-SMX was re-administered. Oral corticosteroid therapy was initiated (Prednisolone,10 mg/kg/24/hr). Corticosteroid was tapered over a 5-week period. Fever resolved within 48- hrs, oral cutaneous lesions and inflammatory syndrome cleared within first week.

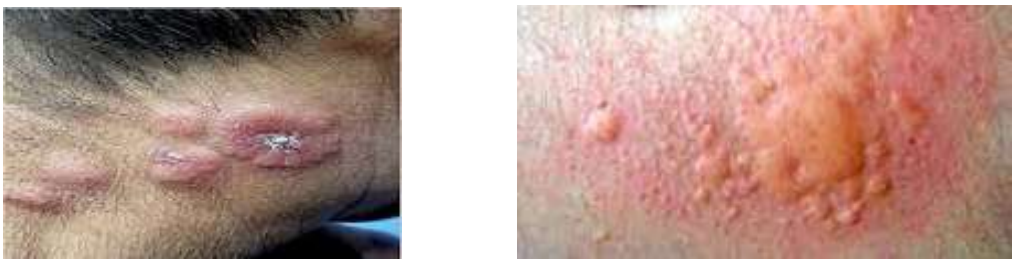

Fig 1: Scattered erythematous patches, pustular and blisters localized on the scale, upper back, chest and palms.

CAUSALITY EVALUATION

To evaluate the relationship between the drug and adverse reaction, causality assessment was done using World Health Organisation- Uppsala Monitoring Centre (WHO -UMC) scale. According to WHO - UMC scale the ADR was classified as probable ADR. The probable ADR includes event of laboratory test abnormality, which is explained by increased WBC with notable increase in polymorphonuclear cells, elevation in ESR, C-RP and α-2-globulin due to the administration of TMP-SMX. Discontinuation of TMP- SMX showed a decrease in the elevated WBC with polymorphonuclear cells and ESR levels as well as the skin lesions started disappearing. This highlights the concept of de-challenge and re-challenge.[5]

DISCUSSION

Drug induced sweet syndrome (DISS) is an uncommon subtype of SS, comprising <5% of cases. Granulocyte colony stimulating factor is the most common culprit, but other drugs have been implicated, including Trimethoprim -sulfamethoxazole (TMP-SMX). TMP-SMX is a combination used to treat infections including urinary tract infections, middle ear infections (otitis media), bronchitis, traveller's diarrhoea and shigellosis (bacillary dysentery).[6] The patient was administered with TMP-SMX 400mg/80mg orally every 12 hrs ,10 days prior to the condition to treat UTI. As observed in our patients, the distribution of skin lesions in DISS most often includes the face, neck, upper trunk and limbs. The patient had cutaneous morphology of scattered erythematous patches, pustular and blisters is consistent with neutrophilic dermal infiltration. The time of onset is similar to that presented in a DISS cases. Fever is considered as one of the diagnostic criteria for DISS as well as classic SS and interestingly our patient was febrile. In terms of laboratory examinations, there observed an elevated WBC with notable increase in polymorphonuclear cells, increase in ESR, C-RP and α-2-globulin which is considered as common laboratory abnormalities in classic and drug induced SS. However, a review of literature suggests that neutrophilia may be more common in TMP-SMX induced SS than compared to other DISS. [7]

In general, TMP-SMX works by inhibiting bacterial synthesis of tetrahydro folic acid, the physiologically active form of folic acid and a cofactor in the synthesis of thymidine, purines and bacterial DNA. It is the first line agent in the treatment of UTI. But in some patients the administration of TMP-SMX can cause erythematous lesions within 1-3 weeks of the drug administration. The pathogenesis of sweet syndrome includes neutrophilic proliferation and maturation, malignant transformation, photoinduction and Koebner phenomenon, cutaneous localization, dysfunctional immune mediators like type 1 helper cells (Th1), interleukins and matrix metalloproteinases (MMPs) and genetic factors mutation including MEFV, FMF and isocitrate dehydrogenase 1 (IDH1). [8]

Nevertheless, given the brisk response to corticosteroid that is observed in most SS patients, corticosteroids are considered to be the first -line treatment. Systemic corticosteroids 0.5 to 1 mg/kg/day for 4 to 6 weeks are the primary treatment for skin lesions. There exist high evidence suggesting that the use of indomethacin had showed a rapid effect if SS does not respond to steroid therapy. Retrospective studies support the usage of acitretin, colchicine and dapsone.[9] Ultimately, treatment should be personalized based upon patient co-morbidities, past medical history and preference. Similar to other cases of DISS, our patient's lesions resolved rapidly with oral steroid treatment.

CONCLUSION

Trimethoprim -sulfamethoxazole induced sweet syndrome is a rare inflammatory, non- infectious skin reaction. It is associated with painful erythematous plaque all over the face, neck and limbs. Sweet syndrome can develop in any age patients but 30-60

years is most common affected age group. Systemic corticosteroid therapy is considered as the first line agent for DISS. The early detection and management of lesions is warranted to avoid the long-term impairment. It is observed in this case that antibiotics can induce hypersensitivity reactions when used for a prolonged duration. TMP-SMX is considered as the first line agent for UTI but is it was observed that TMP-SMX has more potent chance of causing DISS. DISS has retained its defining characteristics while medical advances and scientific discovery have led to a better understanding of disease mechanisms and associations. The clinical similarity of SS with other neutrophilic driven autoinflammatory entities is a challenge in clinical grounds as the diagnostic criteria is not applicable in atypical presentations or overlapping autoinflammatory dermatoses. Clinical pharmacist must be more aware about the usage of TMP-SMX especially in immune compromised patients.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient's parents for publication of this case report.

Declaration by Authors

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