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Terbinafine Induced Stevens Johnson Syndrome Toxic Epidermal Necrolysis Overlap Syndrome

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

SJS-TEN overlap syndrome is a very rare but severe cutaneous adverse drug reaction that is caused by terbinafine administration. The patient was suffering from vulvovaginal for which she was consuming terbinafine which led to the occurrence of cutaneous eruptions, across the right and left lower limbs, face, upper limbs, chest, back, arms, and abdomen, affecting almost the entire body covering 10- 30% of the body surface which makes it to fall under the category of SJS-TEN overlap syndrome. Although considered safe terbinafine may lead to such severe adverse drug reactions, proper precautions need to be taken while prescribing it. Avoid the drug in patients with a history of any drug reactions. The

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main goal of this case report is to bring awareness among healthcare professionals, and to make them vigilant against such severe cutaneous drug reactions caused by terbinafine.

Keywords: Stevens-Johnson syndrome; toxic epidermal necrolysis; cytotoxic t-lymphocytes; terbinafine; body surface area.

ABBREVIATIONS

SJS : Stevens Johnson Syndrome
TEN : Toxic Epidermal Necrolysis
BSA : Body Surface area
ADR : Adverse drug reaction
CTL : Cytotoxic T- Lymphocytes
MHC : Major histocompatibility complex
FasL : Fas ligand
FDA : Food and drug administration
NSAIDs: Non steroidal anti-inflammatory drugs
RBC : Red blood cells
WBC : White blood cells
ALP : Alkaline phosphatase
AST : Aspartate aminotransferase
TNF-α : Tumor necrosis factor-alpha
IV : Intravenous

1. INTRODUCTION

SJS-TEN overlap syndrome is a condition which exhibits symptoms of both SJS and TEN which involves approximately 10% to 30% of the body surface area. It is characterized by epidermal detachment, along with symptoms such as fever and malaise [1]. SJS and TEN are uncommon, severe skin reactions characterized by extensive loss of skin and mucosal tissue, often accompanied by systemic symptoms. In more than 80% of cases, medications are identified as the causative agent for these reactions [2].

SJS and TEN are categorized based on the percentage of skin surface area that is affected:

- Stevens-Johnson syndrome (SJS) typically involves less than 10% of the body surface area (BSA).
- SJS-TEN overlap syndrome is characterized by skin involvement ranging from 10% to 30% of the BSA.
- Toxic epidermal necrolysis (TEN) is characterized by extensive skin detachment, affecting more than 30% of the BSA [2].

The skin and mucous membranes are affected, typically presenting as reddish patches or unusual target-shaped lesions on the trunk. These lesions gradually merge and extend as areas of redness with darkened centers [3]. Oral manifestations are highly prevalent, with mucositis and ulceration observed in nearly all cases, affecting up to 100% of individuals [3]. Ocular involvement is a common occurrence, with varying degrees of severity. It can range from conjunctival redness to the complete shedding of the outermost layer of the eye surface [3]. In the United States, it is estimated that approximately 1.9 adults per million experience TEN each year, while SJS affects approximately 9.3 individuals per million annually [4]. The occurrence of SJS and TEN is relatively rare, with an incidence of approximately one or two cases per one million individuals [5]. The ALDEN score is utilized for the evaluation of causality in SJS/TEN cases. This scoring system relies on six parameters to assess the likelihood of a causal relationship [6]. The time lag between the initiation of drug intake and the onset of the reaction, the probability of the drug present in the body at the time of the reaction, previous exposure to the same or similar drug, DE challenge (discontinuation of the drug after the progression phase of the disease), drug notoriety, and consideration of other potential causative factors are the six parameters used to evaluate causality in SJS-TEN cases [6]. Generally, terbinafine is well tolerated but in rare conditions, severe cutaneous adverse reactions like toxic epidermal necrolysis may occur. The Food and Drug Administration (FDA) has approved terbinafine for the treatment of onychomycosis, a condition characterized by fungal infection of the nails, caused by dermatophyte organisms [7]. Terbinafine is an allylamine compound that acts as a non-competitive inhibitor of squalene epoxidase, an enzyme responsible for converting squalene into squalene epoxide, this leads to the buildup of squalene within the fungal cells leading to their demise [7].

In this study, patient was consuming terbinafine for 15 days to treat vulvovaginal candidiasis following which she developed SJS-TEN overlap syndrome, which is a rare and severe adverse cutaneous reaction. The main objective of this

case report is to bring awareness among medical professionals regarding the potential cutaneous adverse reactions that may occur during the administration of terbinafine. The reporting of terbinafine-induced SJS-TEN overlap syndrome contributes to the pharmacovigilance sector as it helps in monitoring the safety and efficacy of medications, evaluating the risk-to-benefit ratio, and aiding in making critical decisions regarding drug usage.

2. CASE PRESENTATION

A 45-year-old female patient, with a documented history of uncontrolled diabetes and currently on medications, Metformin and Glimepiride, was admitted to a tertiary care hospital. The patient presented with chief complaints of widespread rash accompanied by itching and the presence of bullae (large fluid-filled blisters) throughout the body, fever associated with chills and rigors. Upon examination, the patient was found to be conscious and coherent. The PR was 106 bpm, BP was 130/80 mmHg and cardiac examination revealed normal heart sounds (S1S2). Epidermal denudation, characterized by the loss of the outer skin layer, was also noted. Additionally, numerous erythematous to hyperpigmented patches with well-defined lesions were found across the right and left lower limbs, face, upper limbs, chest, back, arms, and abdomen, affecting almost the entire body. The patient exhibited crusting and erosions on the lips, purulent crusting was observed on the inner canthi of the eyelids.

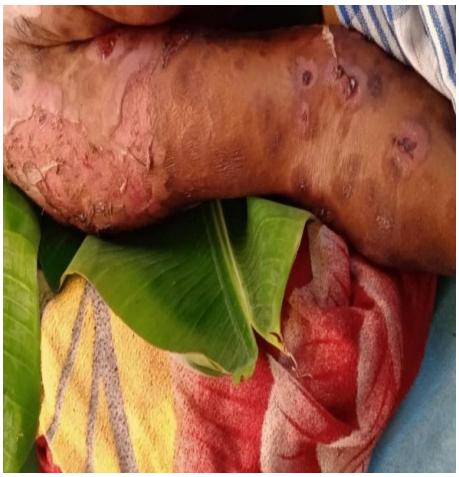

Fig. 1. Presenting cutaneous eruptions on arms

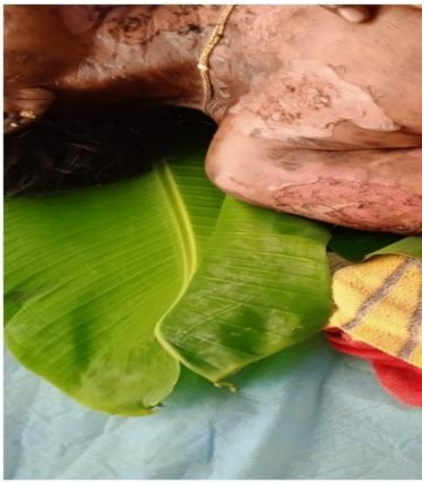

Fig. 2. Widespread TEN-SJS Overlap Syndrome

The laboratory data includes the results of a culture sensitivity test conducted on a sample swab obtained from pus-filled bullae. The culture identified the presence of coagulase-negative Staphylococcus aureus. The detected organism was found to be resistant to erythromycin and clindamycin and was found sensitive to ampicillin, gentamycin and linezolid. The complete blood count reveals: Hemoglobin-9.2 g/dL, RBC-3.47 (in millions per microliter), WBC-6.33 (in thousands per microliter), Neutrophils-93%, Lymphocytes-1.6%, Eosinophils-0.2%, Basophils-0.3%, Hematocrit-30.4%, pH-1.08, Serum urea-3 mg/dL, Serum creatinine-0.45 mg/dL, AST-26 U/L, ALP-65 U/L, Total bilirubin-0.73 mg/dL, Total protein-35.89 g/L, Albumin-2.45 g/dL, Globulin-3.44 g/dL, Sodium-131 mmol/L, Chloride-92 mmol/L. The Alden score for Terbinafine was found to be 4.

Confirmational diagnosis: Based on all the criteria and thorough examination it was confirmed that the patient is suffering from terbinafine-induced SJS- TEN Overlap Syndrome.

Treatment and management: The treatment strategy for this condition involved a comprehensive approach with immediate and ongoing interventions which included injection of Amoxicillin & Clavulanic acid at a dose of 1.2g TID, tablet Cyclosporine 100mg BD, tablet Metformin 500mg BD, pain management by injection Paracetamol 1g BD, steroids such as injection Dexamethasone 8mg IV TID and tablet Prednisolone 20mg OD were given, fluid management was carried out by IV infusion of 2 unit of NS and 2 unit of RL for 7 days. Supportive care measures included O_2 inhalation at a flow rate of 4-6 liters per minute for 1 day, along with the use of Moxifloxacin eye drops, Ciplox eye ointment, Refresh tear drops, saline nasal drops, and Candid mouth paint. Wound care involved the usage of normal saline soaks over crusting, Liquid Paraffin, and Soframycin cream. Banana leaf dressing was employed to provide a cooling effect and alleviate the burning sensation caused by the epidermal eruptions. Terbinafine was discontinued to prevent further damage.

3. DISCUSSION

SJS is a severe condition affecting the skin and mucous membranes, characterized by the presence of flat target-shaped lesions, and the detachment of the epidermis involves less than 10% of the BSA [8]. In cases of TEN, the separation of the epidermis involves more than 30% of the total BSA. In SJS-TEN overlap, the detachment of the epidermis affects between 10% to 30% of the total BSA [8]. The primary reason for the occurrence of most SJS-TEN cases is drug exposure, leading to a hypersensitivity reaction [9]. Roujeau et al. stated that certain medications pose a high risk of causing SJS-TEN when used for a short duration which includes trimethoprim-sulfamethoxazole and other sulfonamide antibiotics, aminopenicillins, cephalosporins, quinolones, and chlormezanone. On the other hand, drugs typically taken over longer periods such as carbamazepine, phenytoin, phenobarbital, valproic acid, oxicam-type NSAIDs, allopurinol, and corticosteroids exhibit the highest risk of triggering SJS, TEN within the initial two months of treatment, followed by a notable decline in incidence [9]. The underlying mechanism behind the severe epidermal detachment observed in SJS, TEN is based on histopathological evidence of keratinocyte apoptosis followed by necrosis. During the early stage of the disease, blister fluid primarily contains CD8+ CTL, indicating an MHC class-I restricted drug presentation that leads to the clonal expansion of CD8+ CTLs [9]. Currently, the most compelling evidence indicates that the cytotoxic molecules FasL and granulysin play a significant role in the widespread apoptosis of keratinocytes observed in SJS and TEN [9]. Terbinafine is an antifungal medication which belongs to the allylamine class of antifungals. Terbinafine is widely used in the treatment of tinea corporis (ringworm) and tinea cruris (jock itch) [10]. The mechanism of action of terbinafine involves the inhibition of squalene epoxidase, an enzyme responsible for the synthesis of ergosterol, a vital component of fungal cell membranes. By preventing the production of ergosterol, which is crucial for fungal cell membrane integrity, terbinafine causes the breakdown of the fungal cell wall [10]. Although limited data is available, there have been reported cases of terbinafine being associated with toxic epidermal necrolysis, a severe skin reaction [11]. The primary approach in managing the condition is to remove the causative agent and provide supportive care [11]. Based on a study conducted by Berthold Rzany MD et al (1994), it appears probable that there is a cause-and-effect relationship between SJS and terbinafine. We can therefore conclude that terbinafine, despite being associated with only minor skin-related adverse effects, should be included in the list of medications capable of causing SJS [12].

In recent findings, cyclosporine demonstrated promising potential in the treatment of SJS and TEN due to its strong antiapoptotic properties [13]. The action of cyclosporine involves the suppression of interleukin-2 production from activated T-helper cells, which in turn inhibits the activation of CD4+ and CD8+ CTLs in the epidermis. Additionally, cyclosporine has demonstrated the ability to inhibit the production of TNF-α [13]. Administering cyclosporine at a dosage of 5 mg/kg/day for 10 days starting from the onset of SJS or TEN has shown potential benefits by reducing the risk of mortality, promoting quicker healing of skin lesions, and possibly enabling an earlier discharge from the hospital [13].

The involvement of multidisciplinary teams consisting of dermatologists, ophthalmologists, and intensivists played a crucial role in the appropriate management of the condition, facilitating a swift and effective recovery. Potential complications observed in this case included the involvement of the oral cavity and its mucosal layers, as well as the presence of ophthalmic crusting. The main challenge in this condition was to prevent and treat a secondary bacterial infection. The family members or attendees have been advised to sanitize their hands before touching the patient.

Healthcare professionals should possess awareness regarding the potential of terbinafine to induce SJS-TEN overlap syndrome. It is crucial to educate patients about their condition, including the risks associated with terbinafine use. Specifically, patients with a history of drug reactions should be advised to avoid the administration of terbinafine altogether.

4. CONCLUSION

The patient presented with fever, cold, generalized rash, skin peeling, itching, and bullae throughout the body. This occurred after taking Terbinafine 200mg for vulvovaginal candidiasis, resulting in SJS-TEN Overlap Syndrome with a BSA involvement of 10-30%. Topical therapies (creams, ointments, ophthalmic and nasal drops) demonstrated positive effects on the patient's condition. Fluid management played a crucial role in the treatment. Although terbinafine is generally considered safe, it caused a severe and rare cutaneous adverse reaction in this case. Healthcare professionals should remain vigilant in recognizing and managing such rare adverse drug reactions associated with terbinafine. The exact mechanism leading to SJS-TEN Overlap Syndrome following terbinafine administration remains unclear, requiring further research.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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