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FLUCONAZOLE-INDUCED TOXIC EPIDERMAL NECROLYSIS

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ABSTRACT

Toxic epidermal necrolysis (TEN) is a rare, and life-threatening condition that affects people of all ages, causing peeling and blistering of skin over the body. The main cause for Toxic epidermal necrolysis is drugs, which can also be triggered by infections and malignancy. Also, the genetic background of the patient, the coexistence of cancer, or concomitant radiotherapy can have an impact on the incidence of SJS(Steven Johnson syndrome) and TEN. Fluconazole is an antifungal medication indicated and belongs to the azole class of drugs, which work by reducing ergosterol synthesis by inhibiting the fungal cytochrome P450 enzyme. After taking the tablet fluconazole 150mg for 5 days a 40-year-old male patient presented with complaints of discharge from eyes & redness for 5 days, Asymptomatic red lesions all over the body for 5 days, painful lesions in the oral cavity for 3 days, Pins and needle sensation over both feet increased while walking, and fever for 1 day. When the patient admitting to TEN, the most important thing is to analyze the patient's past medical history and medication history. The patch test confirmed that the patient has an allergic reaction to T. Fluconazole, hence it was discontinued. Through effective systemic and topical therapy, the patient's condition is improved, also the weekly checkup will be helpful for further monitoring.

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INTRODUCTION

Toxic epidermal necrolysis (TEN) is a rare, and life-threatening condition that affects people of all ages, causing peeling and blistering of skin over the body. It is characterized by mucocutaneous lesions leading to necrosis, erythema, and more or less severe epidermal detachment presenting as blisters and areas of denuded skin. The primary symptoms include fever, stinging eyes, discomfort upon swallowing, and ocular discharge. Typically, these symptoms will cause cutaneous involvement at the presternal region of the trunk and the face, but also the palms and soles. In the secondary phase, large areas of epidermal detachment will develop. Extensive skin loss leads to massive fluid loss and increases the chances of infections. TEN is also known as Lyell's syndrome and it is the most severe form of Steven Johnson syndrome (SJS)[1]

The main cause for Toxic epidermal necrolysis is drugs, which can also be triggered by infections and malignancy. Also, the genetic background of the patient, the coexistence of cancer, or concomitant radiotherapy can have an impact on the incidence of SJS and TEN[2].The most common drugs that cause TEN are Antibiotics (Penicillins, sulfonamides, cephalosporins),Non-steroidal anti-inflammatory drugs(paracetamol and piroxicam), Allopurinol, Anticonvulsants(carbamazepine and phenytoin),and Anticancer agents (Docetaxel and Paclitaxel). If 10 % of the body is affected then it is a minor version of TEN, 10% to 30% of the affecting will be SJS/TEN, and involvement of more than 30% is regarded as Toxic epidermal necrolysis. The reaction can occur or get worse due to the use of one or more drugs and a detailed drug history is essential for identifying the drug that causes TEN[3].

Fluconazole causing toxic epidermal necrolysis is a rare and severe adverse reaction associated with a high mortality rate. Fluconazole is an antifungal medication indicated and belongs to the azole class of drugs, which work by reducing ergosterol synthesis by inhibiting the fungal cytochrome P450 enzyme. Fluconazole is used to treat serious fungal or yeast infections, including vaginal candidiasis, oropharyngeal candidiasis esophageal candidiasis other candida infections (including urinary tract infections, peritonitis, and fungal meningitis.) Other Serious adverse effects associated with fluconazole include agranulocytosis, prolonged QT interval ,anaphylaxis, seizure, toxic epidermal necrolysis, and Stevens-Johnson syndrome. The less common side effects of this drug are headache, nausea, and abdominal pain[4]

OBJECTIVE

An inpatient study of Toxic epidermal necrolysis at the Dermatology department of Karnataka institute of medical sciences (KIMS)hospital Hubli was carried out. Data regarding patient Demographic details, history, Diagnosis, Treatment, and Laboratory tests are collected and analyzed after receiving approval from the Institutional Ethics Committee. The study aims to identify the adverse effect due to fluconazole and understand the management of fluconazole-induced TEN also provide counsel for preventing further complications for the patient.

CASE REPORT

A 40-Year-old male patient was admitted to the hospital with chief complaints of discharge from eyes& redness for 5 days, Asymptomatic red lesions all over the body for 5 days, painful lesions in the oral cavity for 3 days, Pins and needle sensation over both feet increased while walking, and fever for 1 day. The patient was normal 5 days back then he developed discharge from his eyes, yellowish in color, burning sensation, especially on exposure to sunlight. Then he developed asymptomatic red raised lesions initially over the abdomen and chest gradually progressed in size and number, and spread to both upper limbs, face, back, and lower limbs for 5 days. And also, Painful lesions in the oral cavity are associated with difficulty and burning sensation in food intake. On physical examination, his vitals were: Blood pressure of 110/80mmHg, Heart rate:89bpm,Respiratory rate of 16 cycles per minute, and oxygen saturation of 98%.

The patient had a history of Road traffic accident (RTA) 10 years before, for which he had undergone craniotomy, then he developed a seizure following he was put on antiepileptic medication. Initially on T. Eptoin (Phenytoin) 100mg BD for 2 years. He took the medication intermittently, and again he developed seizures; he was advised to take it regularly for 5 years. He is on T. Phenytoin (Eptoin) 100mg OD ,T. Levetiracetam (Levipil) 500mg OD, and now the drug dose reduced to 250mg OD. Now he is seizures free for 4 years but he continuously took the medications. History also added that he developed itchy red lesions over the groin and abdomen for 3 months and visited the nearby hospital, they prescribed Tablet fluconazole 150mg for 5 days before the onset of lesions. He was a chronic alcoholic for 10 years and left 1 year back.

On local examination the patient had multiple well-defined erythematous hyperpigmented macules, Papules, few coalesce to form plaques ,central necrosis, and targeted lesions present all over the body. Conjunctival congestion and purulent discharge from both eyes. Erythematous macules were in palms and soles. Crusting over lower lips and few erosions over the hard palate. Laboratory studies are identified that low Hemoglobin count 12.1g/dl, Normal MCV (97.8ul^3) and MCHC (35.1pg/cell), Increased MCH(34.3g/dl),Sodium (137mEq/l),Potassium (4.4mEq/l),Urea (24mg/dl),Creatinine (0.9mg/dl)levels were normal. ALT(45 U/L) and ALP (129U/L) levels were increased. On the second day of admission ,they advised for a neurological opinion, they suggested that, stop Phenytoin and levetiracetam that already he using. Also, they added that TEN is unlikely due to antiepileptic drugs because the patient is on these medications for 10 years. The patch test confirmed that the patient has an allergic reaction to T. Fluconazole, hence it was discontinued.

The above findings confirmed the Toxic epidermal necrolysis, the treatment started with corticosteroids like Inj. Dexamethasone 2cc OD for 3 days and Triamcinolone gel for topical application. Also, antibiotics were added like Inj. ceftriaxone 1g, Silver sulphadiazine ointment, Mupirocin gel, and T. Norfloxacin BD for 10 days. T. Cyclosporine which is an immunosuppressive agent of 100mg BD and antifungals like clotrimazole cream were given for 8 days. Carboxymethyl cellulose was added to avoid irritation of the eyes. T.Eptoin (phenytoin) and T. Levipil (Levetiracetam) continued for 5 days. The patient's condition started to improve after routine treatment and continuous observation. While discharging the patient's condition was better, discharged with medications such as T. Cyclosporine 100mg BD, Pantop 40mg OD, and Calamine lotion BD. Liquid paraffin BD, T. Norfloxacin BD. Also advised is a 1-week follow-up after, in the OPD department.

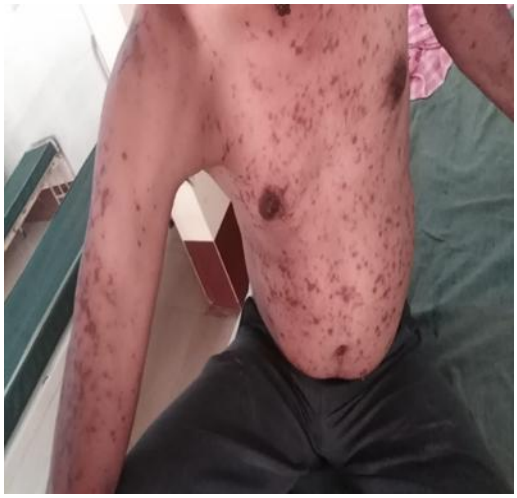

FIGURE 1

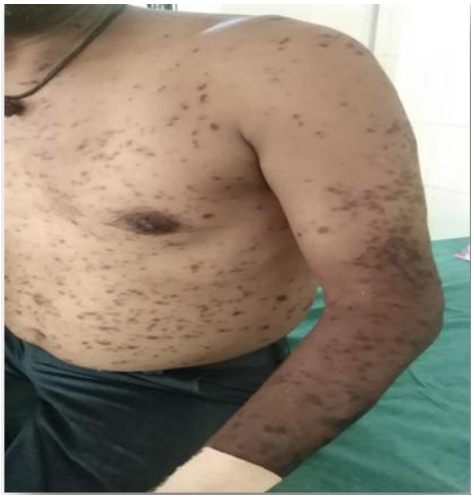

FIGURE 2

DISCUSSION

Toxic epidermal necrolysis is a medical concern as they are associated with high morbidity and mortality, at the same time are unpredictable and vary between individuals. The annual incidence of TEN is 0.5 -0.2 cases per million and the mortality rate of TEN ranges from 25% to 30%.The most common cause of drugs for toxic epidermal necrolysis is antibiotics(37.27%) antiepileptics (35.73%) and non-steroid anti-inflammatory agents(15.93%)[Complications of TEN involve mucosal involvement that will lead to Skin scars, Eye lesions, Dental complications, Genitourinary problems, Infections, Lung involvement, and emotional distress. In most cases the patient admits to the hospital with severe cutaneous rashes, erosions, peeling of the skin, all over the body, and eye involvement .In our cases patient presented with discharge from the eyes, red raised lesions all over the body, and painful lesions in the oral cavity after fluconazole intake[6].

The time interval between the first dose of the drug and the appearance of skin reaction will helpful for determining the causative drug. When the patient admitting to TEN, the most important thing is to analyze the patient's past medical history and medication history[2]. As you can see in our case, the patient was on antiepileptic medications and so chances for phenytoin-induced TEN also can't be avoided. Time taken for phenytoin-induced rashes can be 2 and 8 weeks after initiation of treatment but here this patient is taken this drug for the past 10 years. The time taken for fluconazole-induced toxic epidermal necrolysis is between 4 days to 5 weeks. A diagnosis of drug-induced toxic epidermal necrolysis is mainly confirmed by a patch test and skin biopsy. In our case patch test was carried out and the patient developed an allergy to that.

Toxic epidermal necrolysis is a life-threatening condition and treatment varies with the individual. Supportive care is an essential part of the therapeutic approach also other treatment for TEN involves Antibiotics, Antihistamines, Corticosteroids, and Antiseptic agents are very important. The hospital management included Infection control, pain control, mouth care, preventing dehydration, and eye care[7]. In our case, the causative drug is withdrawn and the patient is managed with supportive care also corticosteroids like dexamethasone, and triamcinolone ointment, and immunosuppressive agents like cyclosporine are given for preventing inflammation. Corticosteroid therapy for toxic epidermal necrolysis is closely monitored because of its chances for slow healing and chances of infection. So ,to prevent the infection in our case antibiotics like ceftriaxone and T. Norfloxacin were added. Topical antibiotics like Silver sulphadiazine ointment and Mupirocin gel were also added to subside the symptoms. Through effective systemic and topical therapy, the patient's condition is improved, also the weekly checkup will be helpful for further monitoring.

CONCLUSION

Fluconazole is the first-line treatment option in several cases of fungal infections and chances of serious side effects are also high. Therefore, careful prescribing and monitoring of the use of this drug must be considered. Proper counseling with the patient will help to know the history and causative drug. The patient must be counseled about his condition and about the importance of notifying the physicians if they develop new or unusual symptoms. Fluconazole consumption should be closely monitored in drug regimen and patient should be counseled about fluconazole side effects.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

ABBREVIATIONS

TEN - Toxic epidermal necrolysis
SJS - Steven Johnson syndrome
MCV - Mean corpuscular volume
MCH - Mean corpuscular hemoglobin
MCHC - Mean corpuscular hemoglobin concentration

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