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Nitrofurantoin Induced Stevens-Johnson Syndrome: A Rare But Serious Adverse Reaction

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ABSTRACT

Stevens-Johnson Syndrome (SJS) a type IV mediated hypersensitivity reaction, it is a rare life- threatening dermatological condition, mucocutaneous reaction often triggered by medications. It affects oral mucosa, skin, eyes, and genitals. Nitrofurantoin, an antibiotic commonly used for urinary tract infections, has been implicated as a potential cause of SJS, though it remains a rare and underreported side effect. Nitrofurantoin-induced Stevens-Johnson Syndrome, although uncommon, should be considered in the differential diagnosis of any patient presenting with acute mucocutaneous symptoms following antibiotic therapy. Early intervention and prompt discontinuation of the offending agent are critical to minimize morbidity and mortality. Treatment strategies may include corticosteroids, immunoglobulins, and other immunomodulating agents but supportive care is often suggested over other therapies as it helps in improving the therapeutic outcomes. In this case, the patient was examined and treated with Cyclosporine and Corticosteroids along with supportive care.

Key words: Stevens-Johnson Syndrome, SJS, Toxic Epidermal Necrolysis, TEN, Granulysin, Nitrofurantoin, Cyclosporine.

INTRODUCTION

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are adverse reactions that affect the mucocutaneous surfaces, causing necrosis and detachment of the epidermis[1]. It is classified as SJS/TEN overlap when 10-30% of BSA is affected[1]. Global data indicates that the incidence of SJS and TEN is between 1.2 and 6 per million patient-years and 0.4 and 1.2 per million patient-years respectively, which corresponds to the limited data available from India[2,3]. Studies also show that Asians and Africans tend to have a 2–3-fold higher incidence of SJS/TEN than Caucasians[4].

Pathogenesis

SJS and TEN were previously assumed to be idiopathic illnesses. However, evidence now suggests that a genetic susceptibility to drug hypersensitivity can cause morbidity[8,9]. Recently, it was shown that granulysin, a cationic protein generated by cytotoxic T lymphocytes and natural killer cells (NK cells), is a key cytolytic factor that causes the extensive keratinocyte necrosis seen in SJS and TEN[10]. The most common substance in SJS and TEN blisters is granulysin, which is thought to function as a cytokine for retinoic acid and other damaging retinoid compounds. Tissue necrosis and sloughing result from the epidermis separating from the dermis when the keratinocytes, which comprise 90% of the cells in the epidermis, die off[9]. Mawson, Eriator, and Karre (2016) simplify the pathophysiology by speculating that the various drugs involved share the ability to interact and work in concert with endogenous retinoids, which causes the liver to accumulate and become damaged, ultimately leading to cholestatic liver dysfunction. As a result, harmful retinoid molecules leak into the bloodstream, causing granulysin to widely trigger cytotoxicity and apoptosis[10].

Class	Examples of drugs in the class
Antibacterials	Sulphonamides(trimethoprim/sulfamethoxazole), penicillins, tetracyclines, quinolones, vancomycin
Anticonvulsants	Carbamazepine, phenytoin, phenobarbitone, lamotrigine Antigout
	Allopurinol
Antimalarials	Chloroquine
Antiretrovirals	Nevirapine, abacavir, protease inhibitors
Antituberculosis	Ethambutol, isoniazid
NSAIDS	Aspirin, piroxicam, diclofenac

Table 1: Drugs that most commonly cause SJS and TEN[8]

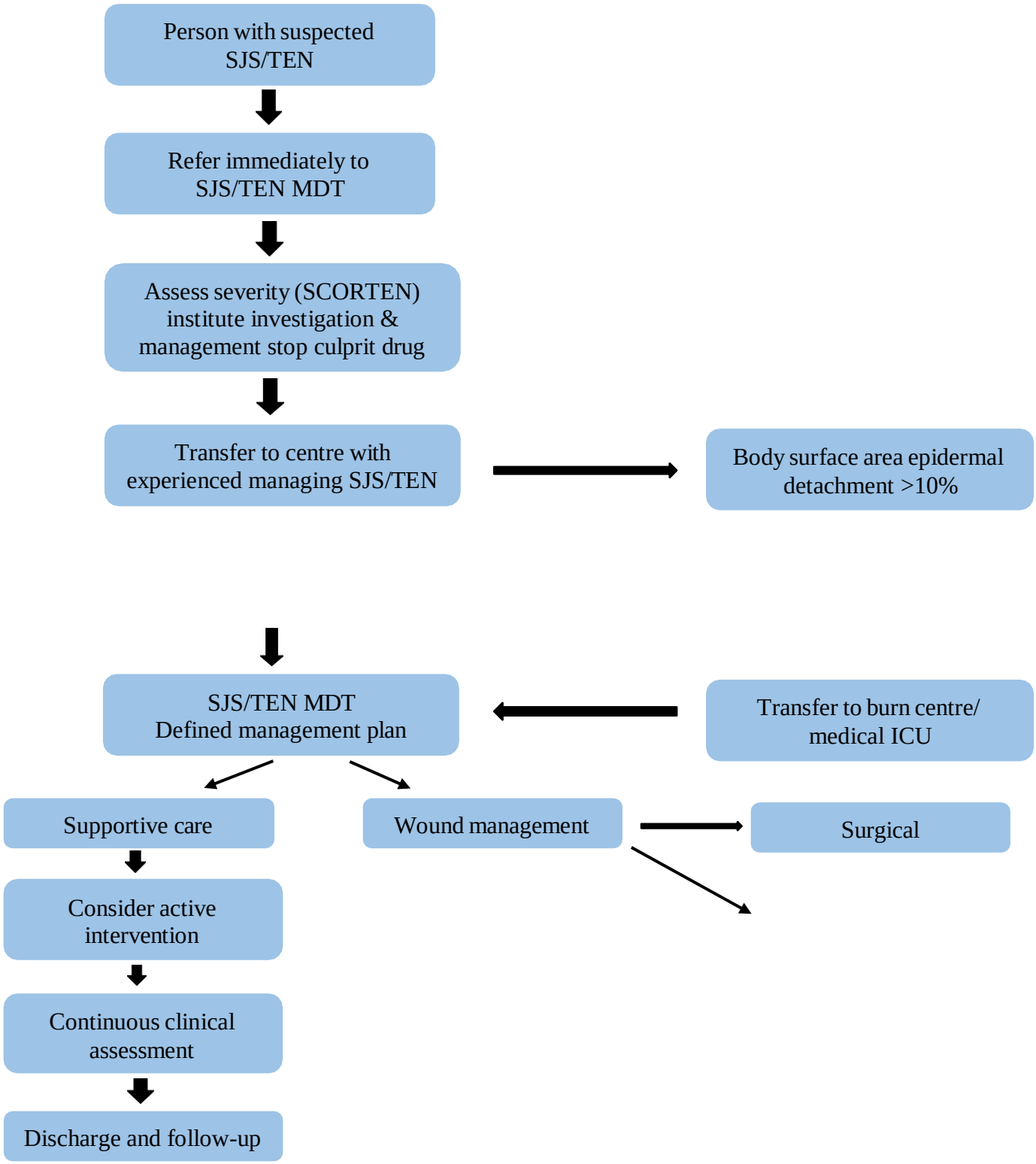
Clinical Manifestations

The clinical features of SJS/TEN are characteristic and the diagnosis is primarily clinical[6,7]. The symptoms of Stevens-Johnson Syndrome characterised by the organs involved are summarized in the **(Table 2)**.

Organ/System	Symptoms
Skin	-Painful red or purple rash -Blisters -Skin peeling (in sheets)
Mucous	-Painful sores or ulcers in the mouth, eyes

Membranes	and genital area -Redness and swelling of mucous membranes
Eyes	-Conjunctivitis (redness, swelling) -Sensitivity to light -Pain or burning sensation in eyes -Vision changes or blindness in severe cases
Respiratory	-Coughing -Shortness of breath -Difficulty breathing -Pneumonitis (lung inflammation)
Gastrointestinal	-Nausea and Vomiting -Diarrhoea -Abdominal pain -Trouble swallowing (dysphagia)
Kidneys	-Reduced urine output -Blood in urine (hematuria)
Musculoskeletal	-Arthralgia
Blood	-Leukopenia, -Thrombocytopenia, -Anemia
Cardiovascular	-Tachycardia -Hypotension

Table 2: Symptoms of Stevens-Johnson Syndrome
2016 Guidelines and Recommendations for the management of SJS/TEN[5]



CASE REPORT

A twenty-four-year-old male patient with complaints of high-grade fever with myalgia, dry cough, left eye pain with redness and watering, oral mucosal ulcers with odynophagia and gingival pain & dysuria and burning micturition since 3 days and painful pruritic scrotal lesions was admitted to the hospital providing tertiary

treatment. His past medical history was unremarkable. Patient had no known drug sensitivities, was not an alcoholic, and did not smoke and no exposures or high-risk behavior. For all the above complaints, previously patient consulted family physician prescribed with Tab Calpol (Paracetamol) 650mg PO BD, Syp Alkanil (Disodium hydrogen citrate and dipotassium hydrogen citrate) 10ml PO BD, Cap Becosules PO BD, Tab Riboflavin PO TID, Tab Niftas SR (Nitrofurantoin) 50mg BD(but patient had this tablet 4 times a day) the symptoms initially improved but 2 days later patient developed ulcers progressed to involve oral cavity, tongue, lips and genitalia.

Figure 1: Crusting and discharge over lips

On examination, patient was alert, coherent, and conscious & crusting and discharge over lips **(Figure 1)** and pseudo membrane seen over lips, purulent conjunctival congestion- positive **(Figure 2)**, 5-8 erosions seen over scrotum and 2 erosions over glans penis, single targetoid lesion over right fore-arm, single vesicle over left wrist, 4 erythematous papules over left palm **(Figure 3)**. Relevant Investigations were done. Viral Screening came out negative and no bacterial growth & pus cells were seen in the Urine Culture and Sensitivity Tests. Based on the physical examination and considering objective evidence patient was diagnosed with Nitrofurantoin induced Stevens-Johnson Syndrome. Patient was treated with these medications mentioned in the **(Table 3)**. After 3 weeks of treatment, improvement was seen in the patient prognosis.

Figure 2: Purulent conjunctival congestion

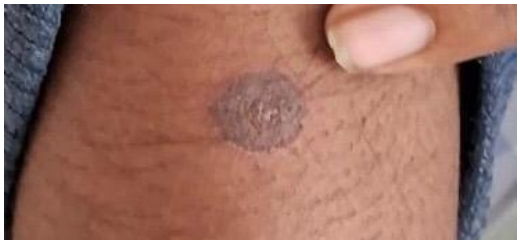


Figure 3: Healing vesicles and erythematous papules

Management

Medication	Dose	Route	Frequency	Indication
Tess Oral Paste	-	L/A	TID	Mouth Ulcers
Normal Saline Gargles	-	PO	TID	Sore Throat
Candid Mouth Paint	-	L/A	TID	Oral Infection
Fluconazole	150mg	PO	Once in a week	Antifungal
Zofer	4mg	IV	SOS	Emesis

Avil	2cc	IV	BD	Allergy
Ascoril LS	10ml	PO	TID	Cough
Moxicep Eye Drops	2 drops	IO	6 times a day	Conjunctivitis
Decadron	2cc	IV	OD	Allergy
Cyclosporine	100mg	PO	OD	Immunosuppressant
Ivermectin	12 mg	PO	BD	Infection
Solumedrol	40 mg	IV	OD	Inflammation

Table 3: IV- Intravenous, PO- Per Oral; L/A- Local Application; BD- Bis die (twice daily); OD- Omni die (once daily); TID: Ter in die (3 times a day); SOS- Si Opus Sit (as needed)

DISCUSSION

Patient came to the hospital with the complaints of high-grade fever with myalgia, dry cough, left eye pain with redness, oral mucosal ulcers with odynophagia and gingival pain & dysuria and burning micturition since 3 days. He had no known comorbidities, no known drug sensitivities, was not an alcoholic, and did not smoke and no exposures or high-risk behavior. He came to the hospital for further management. Physician was advised investigations of Complete Blood Picture, Liver Function Tests, Renal Package II, Viral Screening, Respiratory Panel Test, Urine Culture and Sensitivity, CRP, Serum Electrolytes, e GFR. Patient underwent above investigations, Viral Screening was negative ,Urine Culture shown no bacterial growth & No bacteria and viruses detected by Respiratory Panel Test & Serum Potassium levels were higher than normal which resolved after 3 days of treatment. Based on the objective evidence, clinical condition of patient and opinions from Ophthalmologist and Dermatologist and Infectious Department Opinions, he was diagnosed with NITROFURANTOIN INDUCED STEVENS-JOHNSON SYNDROME. Patient was treated with Tab Fluconazole 150mg OD for 2 weeks and Tab Ivermectin 120 mg BD, Cap. Cyclosporine 100mg PO OD & also steroids Inj. Solumedrol 40mg intravenously for one week, Inj. Decadron 2cc IV OD. The patient and his care takers were given advice on how to proceed with their treatment and patient was counseled about drug adherence.

CONCLUSION

Patient came to the hospital with the complaints of high-grade fever with myalgia, dry cough, left eye pain with redness, oral mucosal ulcers with odynophagia and gingival pain & dysuria and burning micturition since 3 days and diagnosed with Nitrofurantoin induced Stevens- Johnson Syndrome. He had no known comorbidities. Relevant investigations were done. Patient was managed with Immunomodulating agents (Cyclosporine), steroids(Methylprednisolone), Fluconazole and Ivermectin. There was great improvement observed with the therapy of Immunomodulating agents and Corticosteroids in the patient. He had a good prognosis and was stable before discharge.

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