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SJS - TEN Overlap and Delayed Adverse Drug Reaction Following a Traumatic Head Injury

Dr. Nikhat[1], Dr. Shaik Aashik Shahid[2], Dr. Samreen Nishat[3]

[1]Associate professor, Department of Dermatology Venereology and Leprosy, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

[2]Junior resident, Department of Dermatology Venereology and Leprosy, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

[3]Internee, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

1. Introduction

Steven–Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are acute, life-threatening mucocutaneous reactions characterized by epidermal necrosis and detachment. SJS–TEN overlap is defined by 10–30 % body surface area (BSA) of involvement and TEN by >30 %.[1]

2. Presentation of Case

Presenting a case report of SJS-TEN overlap following administration of phenytoin for 4 days as a prophylactic to prevent further episodes of seizures after a head injury. A 73 years old male patient residing at Kokapet, is a carpenter by occupation. The patient had a fall at home and sustained injury on the right side of the head and presented to the casualty. The patient was conscious, coherent and co-operative. The patient is not a known case of diabetes, thyroid disease, or TB. He is a known case of hypertension but not on any medications. The patient has been a chronic alcoholic for 40 years (half bottle per day). Surgical history was not significant. He had an episode of generalised tonic-clonic seizures after injury on his head. He also had vomiting, headache and raised intracranial pressure. The patient had bleeding from the right ear which continued for 4-5 days. The patient was given phenytoin for 4 days as a prophylactic measure following the seizure episode. Neurological examination (reflexes, sensory, motor examination), and vitals were within normal limits. Ophthalmological examination was normal and pupils were reactive to light. All other systemic examinations (C.V.S., Respiratory, G.I.T.) were also normal. CT brain was normal and the cause of seizures remained unknown.

One month later, the patient was referred to dermatology OPD for complaints of itching and rash all over the body since 3 days, difficulty in swallowing food since 3 days, cough since 3 days and fever since one day.The patient reported that he had taken a 4-day course of phenytoin following an episode of seizures post the head injury. On history taking, patient complains of pruritus, rash, redness and burning of eyes, and burning micturition for one week. Pruritus was moderate with no diurnal variation. Rash was sudden in onset, gradually progressive in nature. The rash was erythematous (red) which turned hyperpigmented (black) within 3-4 days time. The patient also complained of skin tenderness on the rash.

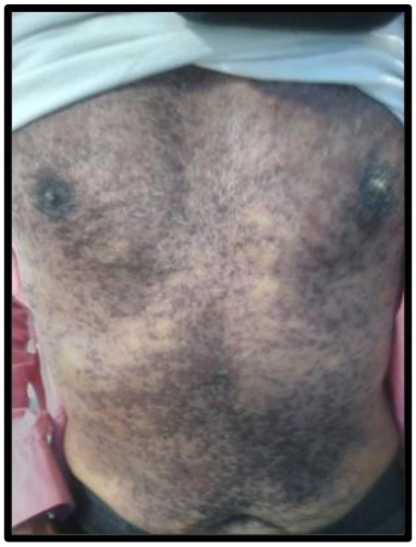
On cutaneous examination proper, the patient had cutaneous necrosis, atypical target like erythematous macules with dark purpuric centres symmetrically distributed all over the face, neck and trunk. Blisters on an erythematous base were widespread on the back, chest, abdomen, face, upper limbs and thighs. Oral erosions and secondary infection in the oral cavity and candidiasis on the tongue was present. Genitals and nails were normal. The patient also had crusted, erosive, hyperpigmented, edematous lips and swelling in the perinasal area. Erosive stomatitis and conjunctivitis were also seen. Bilateral conjunctival injection was present. Pseudo nikolsky sign was positive. A clinical diagnosis of phenytoin induced- Stevens Johnson Syndrome was made and the patient was admitted to the ICU.

The patient was started on Inj. Dexamethasone 2cc I.V. to halt the progression of the disease, I.V. antibiotic (Linezolid) and symptomatic treatment was given. IV fluids and protein powder supplements for nourishment were given. Liquid paraffin for local application on the rashes was advised. Proton pump inhibitors, antacids and cough syrup were given. Oral, topical antifungals were given for candidiasis. Benzocaine gel and triamcinolone acetonide buccal paste for local application on lips. Wet gauze was applied on the lips. Betadine gargles were advised. A nasogastric tube was put because the patient was not able to feed. The patient was advised to rest on rubber sheets. The patient was monitored for BP, GRBS and serum electrolytes.

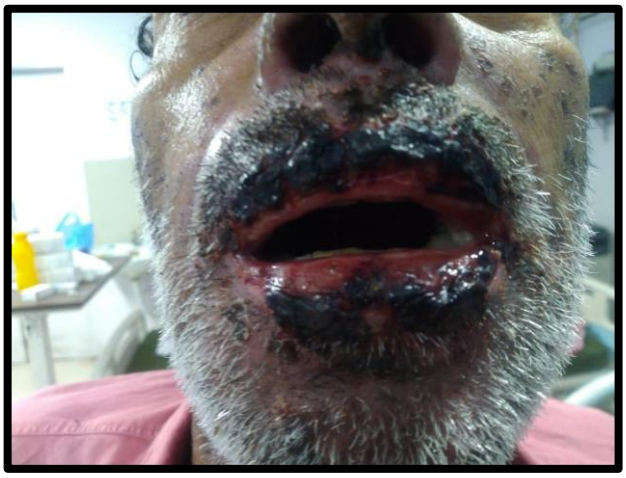
Investigations like complete blood picture, PT, INR, APTT, viral markers (HIV 1&2, HbsAg), complete urine examination, random blood glucose levels, RFT, LFT, blood urea, serum creatinine, serum electrolytes were done. All the investigations were within normal limits.

The patient was admitted for 4 days. The patient had improvement in symptoms within 2 days. Pruritus, rash, redness of eyes and oral lesions began to resolve. There was decreased crusting and SCORTEN score was 1.

Hyperpigmented macules on the nose and nasolabial area
Crusted and erosive lesions on the lips



Diffuse hyperpigmented macules on the trunk



Crusted and erosive lesions on the lips

3. Discussion

SJS and TEN are classified as severe cutaneous adverse reactions (SCAR), a subcategory of adverse drug reactions (ADR).[2] Incidence of SJS and TEN is estimated to be approximately one to six cases per million person-years. It can occur at any stage, with the incidence increasing after the fourth decade.[3]

The etiology can be (1) infectious, (2) drug-induced, (3) malignancy-related, and (4) idiopathic.[4]

Strong drug reaction associations were documented for nevirapine (relative risk (RR)>22) and lamotrigine (RR>14), and weaker associations for sertraline (RR=11[2.7-46]), pantoprazole (RR=18[3.9-85]), and tramadol (RR=20[4.4-93]).Strong associations were confirmed for anti-infective sulfonamides, allopurinol, carbamazepine, phenobarbital, phenytoin, and oxicam-NSAIDs, with some changes in relative numbers of exposed cases. Thus, many cases were still related to a few “old” drugs with a known high risk. The risk was restricted to the first few weeks of drug intake. The use of such drugs as first-line therapies should be considered carefully, especially when safer alternative treatments are available.[5]

Phenytoin, being one of the mainstays of treatment for a variety of seizure disorders, is extensively used in most of the countries and is cost-effective also. It is also among the drugs causing the highest rate of cutaneous adverse reactions. Hypersensitivity to phenytoin is not unusual.[6]Adverse drug reaction accounts for a number of hospital admissions around the world.[7]SJS may have been caused by the anticonvulsant drug phenytoin. Phenytoin induces cytochrome enzymes and produces oxidative reactive intermediates. This could have triggered SJS. [8] Few studies have reported a relation between (HLA-B)*1502 and phenytoin-induced SJS/TEN.[9, 10] Many published case reports documenting drug-induced TEN in patients treated with phenytoin were found; these case reports described severe and life-threatening dermatological reactions.[11, 12, 13, 14]The Naranjo adverse event probability scale was used in some of these reports to assess the correlation between phenytoin therapy and TEN.[15]

A prospective case control study was once conducted and the following consensus classification in five categories was proposed:

- Bullous erythema multiforme: detachment below 10% of the body surface area plus localized "typical targets" or "raised atypical targets";
- Stevens-Johnson syndrome: detachment below 10% of the body surface area plus widespread erythematous or purpuric macules or flat atypical targets;
- Overlap Stevens-Johnson syndrome-toxic epidermal necrolysis: detachment between 10% and 30% of the body surface area plus widespread purpuric macules or flat atypical targets;
- Toxic epidermal necrolysis with spots: detachment above 30% of the body surface area plus widespread purpuric macules or flat atypical targets; and
- Toxic epidermal necrolysis without spots: detachment above 10% of the body surface area with large epidermal sheets and without any purpuric macule or target.[16]

A case-control study reported that the short term use of phenytoin increases the risk of SJS and TEN for a period of less than 8 weeks. In such case, the offending drug should be withdrawn.[17] The time between the 1st administration and development of SJS/TEN is 1-4 weeks in majority of the cases.[18]

Most cases have symptoms like persistent fever, burning or stinging eyes, and discomfort or difficulty swallowing. A pus-producing (purulent) cough may also occur. Such symptoms may precede the development of skin involvement by a few days.[2]

The initial skin symptom is often the development of a superficial reddening of the skin (erythema) or reddish spots on the skins (macules) that rapidly spread and come together (coalesce) to form a rash. In some cases, these lesions may resemble a target or bull's eye, so-called "target" lesions. A rash often first develops on the upper chest, face, and the palms and soles. The rash may be itchy (pruritic) or painful. Blisters appear on the confluent eruption leading to detachment of the skin and leaving erosions.[2]

Blisters may form on various external and internal mucous membranes of the body including the lining inside of the mouth (stomatitis), nose and genitals. Blisters can cause pain and lead to erosions and bleeding. The lips and the inside of the mouth may develop mucosal lesions that are extremely painful and may make eating difficult. Lesions in the genitourinary tract can cause diminished urine flow (dysuria). [2]

The eyes may also be affected. Affected individuals may experience pain and reddish discoloration in the whites of the eyes. Conjunctivitis is common. Affected individuals may have photophobia and blepharitis.[2]

Skin and mucous membrane are involved. Eventually, epidermis may detach from the underlying layers, exposing the underlying layers of skin. Scarring and secondary infection may occur. Patients may develop sepsis. [2]

A disease severity scoring system called SCORTEN (Score of TEN) has been established to help physicians assess the severity of illness in people with SJS and TEN. The more points a patient has, the higher is the risk of fatality.[2] Severity-of-illness and the risk of death of patients with TEN and related disorders can be accurately predicted at admission in a referral unit by the SCORTEN.[19]

Severity-of-Illness Score for Toxic Epidermal Necrolysis (SCORTEN)

Risk Factor*	Score	Score
	0	1
Age	< 40 years	≥ 40 years
Associated cancer	No	Yes
Heart rate (beats/minute)	< 120	≥ 120
Serum blood urea nitrogen	≤ 28 mg/dL (10 mmol/L)	> 28 mg/dL (10 mmol/L)
Detached or compromised body surface	< 10%	≥ 10%
Serum bicarbonate	≥ 20 mEq/L (≥ 20 mmol/L)	< 20 mEq/L (< 20 mmol/L)
Serum glucose	≤ 250 mg/dL (≤ 13.88 mmol/L)	> 250 mg/dL (> 13.88 mmol/L)

*More risk factors indicate a higher score and a higher mortality rate (%) as follows:
0–1 = 3.2% (CI: 0.1 to 16.7)
2 = 12.1% (CI: 5.4 to 22.5)
3 = 35.3% (CI: 19.8 to 53.5)
4 = 58.3% (CI: 36.6 to 77.9)
≥ 5 = > 90% (CI: 55.5 to 99.8)
CI = confidence interval.[20]

Treatment is primarily symptomatic and supportive.Stop the offending drug. Fluid replacement with electrolytes is critical and should be administered immediately. Blood products and supplemental nutrition are given as needed. Antibiotics may be given to control infection. Wound treatment and dressing should be conservative.[2] Initiation of disease specific therapy like corticosteroids, cyclosporine, I.V. immunoglobulins, plasmapheresis, granulocyte colony stimulating factor and other drugs like N acetyl cysteine, cyclophosphamide, thalidomide, pentoxifylline. Pulmonary and ophthalmic care should be taken.[21] Oral hygiene is necessary and a disinfectant mouthwash is beneficial. Lips may be treated with appropriate ointments. In severe cases, affected individuals may not be able to eat, requiring the use of a nasogastric tube. For individuals with eye involvement, treatment may require continued lubrication of the eyes, topical antibiotics, and surgically separating adhesions. [2]

The mortality rate mainly depends on the age and health of the patient, and the rates can range from 30% to 100%. Individuals at the opposite ends of the age spectrum are usually fatal cases.[22, 23] A case was previously reported in which phenytoin caused both myocarditis and SJS in the same patient which is very rare and can lead to increased morbidity and mortality.[24]Another study included 154 patients with antiepileptic-induced severe cutaneous adverse drug reactions (SCARs), including SJS/TEN, found that nonaromatic antiepileptics, e.g., valproic acid and topiramate were safe alternatives for patients with phenytoin- or carbamazepine-induced SCARs.[25]

4. Conclusion

We are reporting this case in which, even after the drug phenytoin was stopped, the patient had an adverse drug reaction (SJS-TEN overlap). However, the prognosis was good. Early recognition and prompt treatment improves the prognosis and outcome.

Phenytoin should be avoided and replaced by other anticonvulsants such as valproic acid, topiramate, levetiracetam, and zonisamide.[8] If phenytoin is prescribed, patient should be educated regarding the possible adverse drug reaction associated with it.

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