



## Drug Induced Toxic Epidermal Necrolysis - It is Phenytoin

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### Abstract

Toxic Epidermal Necrolysis (TEN) is a severe, devastating, and potentially life-threatening mucocutaneous reaction associated with the use of some medications such as phenytoin. Phenytoin being the most widely used antiepileptic drug, constitutes 13.37% of the drug induced cases of TEN. We present the case of a 44 years old male with history of type 2 diabetes mellitus, hypertension and old cerebrovascular accident who was prescribed phenytoin for control of seizures. He presented with acute febrile maculopapular rash and difficulty in swallowing three weeks later after introduction of phenytoin. The rash became diffuse and exfoliative to involve 60 - 70% of body surface area. Despite discontinuation of the drug at day 2 and all supportive measures the patient died due to sepsis and multi organ dysfunction.

**Keywords:** Toxic Epidermal Necrolysis; Phenytoin; Maculopapular Rash

### Introduction

Toxic Epidermal Necrolysis (TEN) is a rare and potentially life-threatening condition with an overall mortality rate of 20 - 30%. TEN is characterized by the detachment of the epidermis from the dermis. It is a drug-induced reaction and the most common causative agents include sulfonamides, barbiturates, pyrazolones, and antiepileptics. Steven Johnson syndrome (SJS) and TEN are reported as related manifestations of the same mechanism with different grades of severity of epidermal necrosis [1]. 95% of the patients with TEN have the history of medication use. Phenytoin constitutes 13.37% of the documented drug-induced SJS-TEN cases [2]. Phenytoin is a widely used medication for common types of epileptic seizures. Time taken for phenytoin induced cutaneous rashes can be between 2 and 8 weeks after initiation of treatment and may progress despite discontinuation of the drug. Withdrawal of the causative drug and supportive care are the cornerstone of management of TEN. Various immunomodulatory treatments for SJS and TEN have been proposed, such as glucocorticoids, intravenous immunoglobulins (IVIG) and cyclosporine. We hereby present a 44 years old case of type 2 diabetes mellitus and hypertension who developed TEN as a result of phenytoin which was prescribed to him for seizures. Despite discontinuation of the drug, severity of drug reaction increased, and the patient succumbed to death as a result of sepsis and multi organ dysfunction.

### Case Report

A 44 years old male presented to our hospital in the month of December 2017 with chief complaints of continuous fever for 7 days along with diffuse, maculopapular rash from day 2 onwards. He also complained of poor oral intake due to difficult swallowing. He was suffering from type 2 diabetes mellitus and hypertension for which he was on regular medication. He used to smoke bidi and consume alcohol occasionally. Two weeks prior to this visit, he was admitted in view of three episodes of generalized tonic clonic sei-

zures. He was loaded with intravenous phenytoin sodium 1 gram after which his convulsions were controlled. On evaluation he was normotensive, found to have normal blood parameters including glucose, serum electrolytes and calcium. MRI brain revealed multiple chronic lacunar infarcts in bilateral basal ganglia and right parietal lobe along with age related atrophy. He was discharged thereafter on tablet phenytoin 300 mg, aspirin 75 mg, atorvastatin 40 mg and advised to continue his antihypertensive and oral hypoglycemic medication.

At the present visit, there was no history of convulsions, headache. He did not complain of bleeding from any site. On examination he was conscious and oriented. He was febrile with temperature of 102°F and had mild pallor. His blood pressure was 130/80 mm Hg, pulse 140/mt, respiratory rate 30/mt and SpO<sub>2</sub> 97% room air. Tongue was dry and coated. He had diffuse maculopapular erythematous extensive rash on face, neck and whole body, however there was no eschar. Systemic examination was unremarkable. There was no neurological deficit. A probable diagnosis of type 2 diabetes mellitus, hypertension, old cerebrovascular accident, seizure disorder with acute febrile exanthema was made. Routine investigations (Table 1) were sent on day 1 which revealed anemia, leukocytosis, thrombocytosis and raised ESR. Blood glucose levels along with liver and kidney function were deranged. On day 2, rash became extensive and diffuse to include oral cavity along with conjunctival congestion, lip crusting and cheilitis. There was slough over tongue, buccal mucosa and posterior pharyngeal wall was congested. Dermatologist opinion was suggestive of DRESS (Drug reaction with eosinophilia with systemic symptoms) or viral rash. Other relevant investigations like dengue IgM, typhidot IgM, scrub IgM, malarial antigen and blood culture were also sent which were negative. Thus, high possibility of DRESS with sepsis and multi organ dysfunction (MODS) was considered. Therefore phenytoin, ramipril, aspirin and statin were withheld.

Parameter	DAY 1	DAY 3	Day 4
Hb/TLC/ PLATELET/ ESR	8.9/17000 /5.58/72	8.5/19000 /5.55	8.3/23300 /4.83
Sbil/SGOT/ SGPT/ALP	0.3/828 /526/773	0.2/738 /561/713	0.4/130 /260/451
BU/CREAT	119/3.4	132/3.6	226/4.8
RBS	255	170	
DENGUE IgM		Negative	
SCRUB IgM		Negative	
TYPHIDOT IgM		Negative	
MP ANTIGEN		Negative	
Blood culture			Sterile

**Table 1:** Laboratory investigations at day 1, day 3 and day 4.

On day 2, he was started on intravenous levetiracetam 500 mg 12 hourly, ceftriaxone 1gram 12hourly, premix insulin regimen and tablet amlodipine 5 mg through RT. Mouth care was provided with disinfecting mouthwashes and ointments. Eye care with lubricant eye drops was provided. On day 3, condition deteriorated, fever persisted and there was extensive peeling of skin on back and buttocks. Review dermatology opinion suggested TEN as there was exfoliation of epidermis with involvement of 60 - 70% body surface area. Thus, a diagnosis of phenytoin induced TEN with sepsis and multi organ dysfunction was made. Total leucocyte count increased and hence antibiotic was stepped up to intravenous meropenem 1 gram 8 hourly along with dexamethasone 8mg. In case of deteriorating state of the patient, IVIG indent was sent. By day 4 he became dyspneic. Respiratory examination revealed bilateral mid inspiratory crepts and chest radiograph showed bilateral middle and lower zone in-homogenous infiltrates. On day 5 breathlessness worsened, mean arterial pressure declined (MAP = 60 mm Hg) and SpO2 on room air was 76%. Blood pressure was not fluid responsive and infusion noradrenaline 0.05U/kg/hour was initiated. Bed-side echocardiography and echocardiogram showed sinus tachycardia. Blood pressure did not escalate even after vasopressors and patient succumbed to death due to sepsis, multi organ dysfunction and cardiorespiratory failure.

## Discussion

TEN is a severe and devastating mucocutaneous reaction associated with the use of some medications such as phenytoin. It is characterized by rapidly developing extensive erythema, necrosis, and detachment of the epidermis and mucous membranes that result in severe and fatal systemic complications such as sepsis if untreated as in our case. Cases with epidermal detachment involving < 10% of BSA are considered SJS while those with 30% or more are classified as TEN. The SJS-TEN overlap is an intermediate condition where skin detachment involves 10 - 30% of BSA [3]. SJS and TEN are severe and life-threatening conditions with mortality rates of 1 - 5% and 25 - 35%, respectively [4]. Our case developed extensive exfoliation of skin involving more than 30% BSA and was labelled as TEN.

The major causative drugs that were responsible for causing such mucocutaneous reactions are antimicrobials (37.27%), anti-epileptics (35.73%) and non-steroidal anti-inflammatory drugs (15.93%), carbamazepine (18.25%), phenytoin (13.37%), fluoroquinolones (8.48%) and paracetamol (6.17%) [5]. Among anti-epileptic drugs carbamazepine and phenytoin are the most common drugs causing 11 cutaneous adverse reactions. A systematic review of drug-induced SJS and TEN among Indian patients concluded that phenytoin is one of the major causative agents for SJS-TEN and it

was implicated in 13.37% of the documented drug-induced SJS-TEN cases [2]. In our case as soon as rash was implicated to phenytoin, it was stopped and instead levetiracetam was introduced.

Usually, the acute phase of the onset of cutaneous eruptions lasts from 8 to 12 days after drug intake. Frequently, TEN and SJS are characterized initially by unspecific signs and symptoms such as fever, stinging eyes, and discomfort on swallowing. Our case developed fever and difficult swallowing first and cutaneous eruption few days later after phenytoin intake. Thereafter, cutaneous manifestations start to appear a few days later; cutaneous involvement typically starts to affect the trunk, face, palms, and soles. More than 90% of cases include mucocutaneous involvement of the buccal, genital, and/or ocular mucosa [6].

At present, there is no effective specific therapy for TEN [7]. Supportive care until epithelium regeneration is the cornerstone of TEN management. Despite the lack of proven efficacy, systemic high dose steroids have shown beneficial results. Early administration of high-dose immunoglobulin (3 g/kg total dose given over 3 - 4 days) should be initiated [8].

## Conclusion

We as clinicians should keep high index of suspicion for any mucocutaneous eruption after introduction of potential causative drugs. Early diagnosis with the prompt recognition and withdrawal of such drugs is essential for a favourable outcome.

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