A Phenytoin Induced Toxic Epidermal Necrolysis (TEN) – A Case Report

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ABSTRACT

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Toxic Epidermal Necrolysis (TEN) is a rare, potentially life threatening dermatological condition that is usually induced by medications. The usage of anti-convulsants like carbamazepine, phenytoin, lamotrigine, phenobarbital, fosphenytoin are associated with high risk for occurrence of TEN. A 36 year old female patient was brought with the history of Phenytoin induced Toxic Epidermal Necrolysis. This patient was prescribed tablet phenytoin 300mg/day, 100mg in the morning and 200mg at night for her generalized tonic-clonic seizure disorder and patient had history of using the drug for a period of 28 days. Patient developed macular rashes on the skin and consulted a general physician who prescribed her with cetirizine 5mg, bid. The drug phenytoin was continued till she visited Government District Head Quarters Hospital,Udhagamandalam in spite of treatment with cetirizine the rashes spread all over the body with an additional ocular redness with discharge. This case report describes the management of this patient.

Keywords: Toxic epidermal necrolysis, phenytoin, tonic-clonic seizures, anti-convulsants.

INTRODUCTION

Toxic epidermal necrolysis (TEN) also known as 'Lyell's syndrome' is an unpredictable, life threatening drug reaction causing 77-95% of cases[1, 2]. Both Stevens Johnson Syndrome (SJS) and TEN are characterized by epidermal detachment and erosive mucosal lesions but after years of debate, both are now considered to be the same condition but differ in severity of cutaneous involvement[3]. The percentage of epidermal detachment is the primary differentiating factor, SJS presenting with <10% epidermal detachment and TEN presenting with >30%[4]; while cases between 10% and 30% of involvement are defined as SJS-TEN overlap[5]. Incidence rate of Phenytoin induced mucocutaneos reactions is 13.37% in India[6]. More than 90% of SJS and TEN cases occurred in the first 63 days of anti- epileptic drug use[7]. TEN presents with erythematous macules or ill-defined erythema, Nikolsky's sign (rubbing of skin results in exfoliation of the outer most layer) is almost always present. Almost all patients with mucosal reaction develop painful haemorrhagic erosions coated by greyish white pseudo-membranes and crusts in the oral cavity and on the border of the lips[3].

CASE REPORT

A 36 year old female was presented to Government District Headquarters Hospital (GHQH), Udhagamandalam, to emergency department with the complaints of rashes spread all over the body associated with pain, swelling of lips, tongue and ocular redness with discharge. The patient had a two year history of a fall and injury to the head. The patient had first episode of generalised tonic-clonic seizures and was admitted into the hospital for duration of 3 days. On day 4, the patient was discharged and her discharge medication include – Tab. Phenytoin 100mg (1-0-2) to prevent further convulsions, Tab. Ranitidine 150mg (1-0-1) to prevent gastric discomfort and Tab.B-complex (vitamin B_1-2mg; B_2-2mg; B_6-0.5mg; Niacinamide-25mg; Calcium-1mg) (0-0-1) as vitamin supplement.

The patient was asked to come for follow-up visit to out-patient department after one month. Patient experienced the rashes all over her body after the consumption of Tab. Phenytoin 300mg/day for 28 days and was presented to the hospital, on the day of admission (Day 1) the patient was conscious, oriented and afebrile and her blood pressure was 110/70 mmHg. Upon physical examination, the patient showed the widespread of mucocutaneos rashes all over the body. The suspected drug, phenytoin was advised to discontinue, and was kept under observation. The patient was treated and the medications prescribed are Inj. Ceftriaxone-2cc (250mg/vial) (1-0-1), Tab. Chlorpheniramine maleate 4mg (1-0-1), Tab. Alprazolam-0.25mg (0-0-1), Inj. Ranitidine-(50mg/2ml) (1-0-1) as prophylactic to prevent epigastric distress caused by chlorpheniramine maleate and the patient was given saline dressing care for her rashes. The patient's urine I/O at the end of the day are 1050ml and 900ml respectively. Blood was drawn from the patient for laboratory investigation.

On the second day, laboratory investigation reports (Table-1) were obtained. The patient's blood pressure was recorded as 110/70 mm Hg and her urine I/O at the end of the day were 1000ml and 800ml respectively and continued the same treatment.

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On the third day, the patient presented with cough as new complaint. On examination, the patient was afebrile, her cardiovascular and respiratory sounds were found to be normal and abdomen was soft. In addition to her previous day's treatment she was prescribed with Inj. Dexamethasone - 8mg (1-0-1) to reduce allergic and inflammatory process, Inj. Chlorpheniramine maleate 10mg (1-0-1) for her rashes, Cough syrup (Chlorpheniramine maleate-3mg; Ammonium chloride 130mg; Sodium Citrate - 65mg; Menthol 0.5mg in 50ml bottle) - 5ml (1-0-1) for her cough.

On day 4, the patient was transferred from emergency department to female medical ward. Her blood pressure was recorded as 130/80 mmHg. The patient was seen by the dermatologist who observed erythematous macular rashes with purpuric centres in more than 30 percent of the body and diagnosed her condition as Toxic Epidermal Necrolysis (TEN) based on the clinical findings and advised to check the levels of serum electrolytes and serum protein and stop using all the antibiotics. The patient received the following medication along with saline dressing for the rashes. Ringer's Lactate solution 3 pints intravenously as electrolyte supplement as the patient is not able to take food through oral route,Inj. Dexamethasone- 8mg (2cc) (1-0-1), Inj. Ranitidine-50mg/2ml (1-0-1) with Chlorpheniramine maleate were administered. Patient's urine I/O at the end of the day was 1800ml and 1000ml respectively.

On day 5, the patient's general condition was fair and her cardiovascular and respiratory sounds were normal. Her Blood pressure was 110/70 mmHg urine I/O at the end of the day were 750ml and 700ml respectively and the patient received the same medication as that of the previous day.

On day 6, at 8 am the patient's general condition was fair and her cardiovascular and respiratory sounds were normal. Her Blood pressure was 110/70 mmHg and the patient received the same medication as that of the previous day.

Table 1: Laboratory investigation report of the patient obtained on second day of admission

Clinical Parameter	Value in patient	Normal Value
Hemoglobin	10.8g/dl	12-16g/dl
Total WBC Count	$8.7*10^3$ cells/mm^3	$3.2-9.8*10^3$ cells/mm^3
Differential Count		
Polymorphs	89%	54-62%
Lymphocytes	11%	25-33%
Platelet Count	$265*10^3/mm^3$	$130-400*10^3/mm^3$
RBC's	$3.64*10^6/mm^3$	$3.5-5.0*10^3/mm^3$
Hematocrit	31.5 %	33-43%
Mean Cell Volume	86.5fL	76-100 fL
Mean Cell Hemoglobin	29.7pg/cell	27-33pg/cell
Mean Cell Hemoglobin Concentration	34.3 g/dl	33-37 g/dl
Blood Sugar (Random)	112mgs%	<200mgs%
Blood Urea	32mgs%	20-40mgs%
Serum Creatinine	1.4mgs%	0.6-1.2mgs%
ST-Aspartate aminotransferase (SGOT)	28U/L	0-
35U/LALT-Alanine aminotransferase (SGPT)	17U/L	0-35U/L
Alkaline Phosphates (ALP)	80U/L	30-120U/L
Bilirubin		
Total	0.3mg/dL	0.1-1 mg/dL
Direct	0.2mg/dL	0-0.2mg/dL
Indirect	0.1mg/dL	0.1-0.8mg/dL

On day 7, at 8 am in morning, the patient's blood pressure was recorded as 110/70 mmHg. The patient had complaints of pain all over the body and swelling of lips. According to Modified Hartwig and Siegel Severity (MHSS) Scale, an adverse drug reaction severity scale, this patient was placed at level-5 requiring intensive medical care. Based on this, the patient was referred to Coimbatore Medical College Hospital (CMCH), Coimbatore by the dermatologist to obtain second opinion from dermatologist and neurologist and for further treatment. On the day of referral, she received the discharge medication as Tab. Prednisolone 15mg in the morning and 5mg in the night.

DISCUSSION

SJS and TEN are characterized by rapidly expanding blistering exanthema of purpuric macules and target-like lesions accompanied by mucosal involvement and skin detachment.[8] Mortality rate due to these conditions can reach up to 40%.[9] This patient met the diagnostic criteria for phenytoin induced TEN according to Roujeau's classification.[8] The mucocutaneos reaction experienced by the patient falls under CERTAIN criteria according to World Health Organization scale of assessment and under allergic adverse drug event according to Pharmaceutical Care Network Europe (PCNE) classification of drug related problems. The major causative drugs that were responsible for causing mucocutaneos reactions like TEN, SJS and SJS/TEN 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%).[10] Among antiepileptic drugs (AEDs) carbamazepine (CBZ) and phenytoin (PHT) are the most common drugs causing cutaneous adverse reactions.[11]

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. Aggressive medical management is necessary to ensure the best chance of complete recovery with minimal permanent sequelae. Factors responsible for increased risk of this reaction include the use of higher than recommended dose, more rapid dose escalation and concomitant use of Sodium valproate.[12]

The exact mechanism of SJS/TEN still remains unknown but still the proposed includes involvement of immunological mechanisms, reactive drug metabolites or interactive between these two. Epidermal necrolysis is caused by interactions between CD95 L and Fas (CD95).[13,14] Disseminated keratinocyte death in SJS/TEN can also be due to Granulysin.[13] The studies performed in Taiwan indicate a strong association between HLA-B*1502 allele and phenytoin induced SJS/TEN[15,16] and declared that the allele can be considered as a universal marker for phenytoin induced SJS/TEN, which is not supported by few studies.[17]

This patient was diagnosed with phenytoin induced TEN on day 4 as all other potential causative drugs or infections, including HIV (according to Integrated Counselling and Testing Centre HIV test was non-reactive) were omitted and dermatologist ordered to stop the prescribed antibiotics Inj. Ceftriaxone 2cc (250mg/vial) iv bid which was administered to the patient for three days and prescribed Inj. Dexamethasone 8mg twice daily for 4 days. On 7th day of hospital stay, patient was referred to CMCH, Coimbatore to obtain second opinion from dermatologist and neurologist and for further treatment. Tab. Prednisolone 5mg was the discharge medication. Usage of corticosteroids in this kind of cases is still debatable. Meta-analysis report suggest that usage of corticosteroids for first three days, may reduce mortality without affecting the healing time.[18] Investigation of serum drug concentrations would provide more information, which helps to comment on category of ADR and drug metabolism. Topiramate or Levetiracetam (antiepileptic drugs) will be the treatment of choice for this patients when phenytoin or carbamazepine has induced SJS/TEN.

CONCLUSION

Symptoms of toxic epidermal necrolysis will be cutaneous to start with which leads to extra cutaneous, or mucous membranes and may involve further body systems if not addressed. In this patient, the present condition has been induced by phenytoin which was diagnosed by dermatologist and as the patient needed an intensive medical care according to MHSS scale, she was referred to Coimbatore Medical College Hospital (CMCH), Coimbatore to obtain second opinion from Neurologist and Dermatologist and for further treatment.

As the adverse systemic reactions to antiepileptic drugs (AEDs) are rare and severe, physicians should counsel patients on the importance of notifying their physician if they develop any new or unusual symptoms and patient was provided with 'drug alert card' and was advised to carry it with her whenever she seeks medical attention.

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