Case Report

Fatal phenytoin-induced Stevens–Johnson syndrome in an elderly person with metastatic lung carcinoma

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Abstract

Health-care providers must be cautious about the adverse effects of drugs, especially Stevens–Johnson syndrome, which is a potentially fatal condition. Several drugs are at high risk of inducing Stevens–Johnson syndrome including allopurinol, sulfonamides, cephalosporins, quinolones, phenytoin, carbamazepine, and nonsteroidal anti-inflammatory drugs. Owing to high risk of mortality, management of patients requires rapid diagnosis, identification and discontinuation of the causative drug, and specialized support care.

KEY WORDS: Stevens–Johnson syndrome; Phenytoin; Immunocompromised

Introduction

Stevens–Johnson syndrome (SJS), also known as erythema multiforme major, is assumed to symbolize a range of infections, the most benign type of which is erythema multiforme (EM), whereas toxic epidermal necrolysis (TEN) is the most severe.[1]

The four causative categories are (a) infectious, (b) drug-induced, (c) malignancy-related, and (d) idiopathic.[2] Medication usage is most commonly associated with TEN, with up to 80% of TEN cases being attributed to drug therapy. SJ Syndrome and EM-minor are also related to medications, in up to 57% and 23% of cases, respectively.[3,4]

Antibiotic causative factors include penicillins and sulfa antibiotics. Anticonvulsants including phenytoin, carbamazepine, valproic acid, lamotrigine, and barbiturates have been implicated. The most latest inclusion to probable drug-induced cases include the antidepressant mirtazapine and the TNF-alpha antagonists infliximab, etanercept, and adalimumab.[2] In spite of all therapeutic efforts, mortality is elevated and rises with disease extremity, patients' age, and underlying medical conditions.

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Case Report

A 78-year-old female subject, widowed, belonging to lower socioeconomic status, and hailing from Kalihundi, HD Kote, Mysore, Karnataka, India, reported to the Medicine OPD of KR Hospital, Mysore, Karnataka, India, on July 25, 2014. Her chief complaint was history of rashes and peeling of skin over the face, scalp, chest, abdomen, back, hands, and legs since 3 days. On examination, it was observed that there were multiple targetoid lesions over chest, abdomen, buttock, and both upper and lower limbs. There was also peeling of sheets of skin over the scalp and back with hemorrhagic blisters [involving 25% body surface area (BSA)]. The face was covered with multiple crusted lesions and peeling of the skin. On examination of oral cavity, there were erosions on buccal mucosa and lips. There was chemosis and purulent discharge from the conjunctiva (Figures 1 and 2).

The patient was a known case of carcinoma lung with brain metastasis since 8 months and underwent chemotherapy with tab geftimab (200 mg bd) for 5 months. She underwent radiotherapy for 1 week about 3 months back. Just before the patient developed the presenting complaints, she was on treatment with tab phenytoin for 1 week to treat a single seizure episode. The patient's vital signs and temperature were within normal ranges. The patient's Hb% was 8.2 gm%,

Figure 1: Face covered with multiple crusted lesions and peeling of the skin.

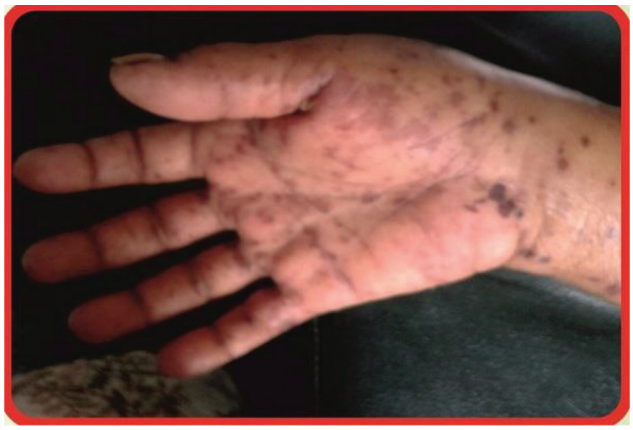

Figure 2: Multiple targetoid lesions over the palm.

WBC: 7.3 cc, RBC: 3.23 cc MCV: 79.3 fL, MCH: 25.4 pg, MCHC: 32 g/dL, FBS:181 mg/dL, PPBS: 261mg/dL. Blood urea, serum creatinine, and serum electrolytes were in normal limits.

Prothrombin time was 15 s. Activated partial thromboplastin time was 32 s. Platelet count was 143,000 L/cmm. Results of liver function tests were normal.

Doppler was done, and there were signs of thrombosis of left superior and inferior femoral veins.

The tab phenytoin was stopped once she developed the SJ syndrome. She was then treated with steroids, anti-infective therapy, anticoagulant therapy, and other supportive measures.

In spite of all this treatment, the patient did not survive.

Discussion

Pharmacovigilance is the science and activities related to the detection, assessment, understanding and prevention of adverse effects, or any other possible drug-related problems. Today, the need for an efficient pharmacovigilance system has been realized more than ever to ensure safe use of drugs. All issues related to safe use of drugs are relevant for everyone whose life is affected by medical interventions.[5]

SJS is one of the most debilitating adverse drug reactions recognized. It was first discovered in 1922 by pediatricians AM Stevens and FC Johnson after diagnosing a child with severe ocular and oral involvement to a drug reaction.[2] SJS and TEN are acute life-threatening conditions.[6] The simplest classification breaks the disease down as follows:

- SJS: A minor form of TEN, with less than 10% BSA detachment.
- Overlapping SJS/TEN: Detachment of 10%–30% of the BSA.
- TEN: Detachment of more than 30% of the BSA.

Both SJS and TEN are debatably included in the same spectrum as EM. This mucocutaneous condition shows similarities in clinical presentation to SJS/TEN but exhibits some distinct differences.[7,8] The mortality rate mainly depends on the age and health of the patient, and rates can range from 30% to 100%. Individuals at opposite ends of the age spectrum, (i.e., the very young and the old persons) are usually fatal cases.[9,10]

Although the majority of cases are idiopathic (without a known cause), the main class of known causes is medication, followed by infections and rarely, cancers.[11] An idiosyncratic, delayed, hypersensitivity reaction has been implicated in the pathophysiology of SJS. Certain population groups appear more susceptible to develop SJS than the general population. Slow acetylators, patients who are immunocompromised (especially those infected with HIV), and patients with brain tumors undergoing radiotherapy with concomitant antiepileptics are among those at most risk.[12] Other factors associated with SJS/TEN are infectious diseases such as those caused by human immunodeficiency virus, herpes virus or *Mycoplasma pneumoniae*, and hepatitis A virus, and noninfectious conditions including radiotherapy, lupus erythematosus, and collagen vascular disease. (HLA)-B12, HLA-B*5801, and HLA-B*1502 are involved with increased risk of developing SJS/TEN.[13]

The case presented here demonstrates that the rash erupted after the administration of tab phenytoin. It is believed that phenytoin induces cytochrome P450 3A and produces oxidative reactive intermediates that are involved in the hypersensitivity reaction.[14] In addition, it is thought that the aromatic chain in the chemical structure of phenytoin and other agents undergo a detoxification pathway mediated by epoxide hydrolases.[15] The patient was also immunocompromised as she was aged; she was on cancer chemotherapy and radiotherapy.

Other studies with phenytoin-induced SJS have been reported in literature.[16–19] So, depending on the seizure type, other antiepileptic drugs can be used, which do not cause this fatal reaction such as valproic acid, topiramate, levetiracetam, and zonisamide.[20]

Conclusion

SJS may have been caused by the anticonvulsant drug phenytoin. Phenytoin induces cytochrome enzymes and produces oxidative reactive intermediates. This could have triggered SJS as the patient was immunocompromised. So, phenytoin should be avoided and replaced by other anticonvulsants such as valproic acid, topiramate, levetiracetam, and zonisamide.

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